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Maternal and Fetal Factors Associated with Labor and Delivery Complications

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MATERNAL AND FETAL FACTORS ASSOCIATED WITH LABOR AND DELIVERY COMPLICATIONS

A Dissertation Presented

by

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DEDICATION

I dedicate this thesis to my late brother, Sandesh L. Gawade

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ABSTRACT

MATERNAL AND FETAL FACTORS ASSOCIATED WITH LABOR AND DELIVERY COMPLICATIONS

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Prolonged second stage of labor, excessive gestational weight gain and cesarean delivery has been associated with adverse maternal and fetal outcomes. Physical activity during pregnancy is a modifiable risk factor which has never been studied among Hispanic women. Gestational weight gain, another modifiable risk factor has only been evaluated as a risk factor for cesarean delivery in two studies among women induced for labor. To date, no study has examined the effect of duration of second stage of labor on intra-ventricular hemorrhage in very preterm births. We examined these maternal risk factors for prolonged second stage of labor, rate of cesarean delivery and fetal outcomes.

The first study evaluated the association between physical activity and duration of second stage of labor. Prior studies regarding physical activity and duration of second stage of labor have been conflicting and none have examined the Hispanic population. During pregnancy, activities such as household chores, childcare, sports and women's occupation constitute a significant proportion of physical activity but have not been considered in prior studies. We examined the association between total physical activity (occupational, sport/exercise, household/care giving, and active living) during pre, early and mid-pregnancy and duration of second stage of labor in a prospective cohort of 1,231 Hispanic participants. Physical activity was quantified using the Kaiser Physical Activity Survey administered during pregnancy. Using multivariate linear regression we did not

find statistically significant association between pre, early and mid-pregnancy physical activity and duration of second stage of labor.

The second study focused on the effect of gestational weight gain on the cesarean delivery rate after induction of labor. The rate of induction of labor (IOL) has more than doubled from 9.5% in 1990 to 22.5% in 2006. Cesarean delivery usually follows a failed IOL and is associated with maternal and fetal morbidity. One of the two studies evaluating the effect of gestational weight gain on the rate of cesarean section in patients undergoing IOL was restricted to women with normal Body Mass Index (BMI) and the other was subjected to bias because more than half of the patients were missing BMI data. Therefore, we evaluated the effect of gestational weight gain on the rate of cesarean delivery after labor induction. In a retrospective cohort study design, using data from May 2005 to June 2008 and a multivariate logistic regression we found a 13% increase in risk of cesarean delivery with 5 kg increase in gestational weight gain.

Finally, we evaluated the effect of mode of delivery and duration of second stage of labor on intra-ventricular hemorrhage (IVH) among early preterm births. IVH is a serious complication associated with preterm birth and important predictors of cerebral palsy and neurodevelopmental delays. Prior studies on this relationship in early preterm births are sparse. In a retrospective cohort study of newborns born less than 30 weeks or less than 1500 g between May 2003 and August 2008, we found an increase in risk of IVH after vaginal delivery. However, duration of second stage of labor had no significant effect on risk of IVH.

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CHAPTER 1

PHYSICAL ACTIVITY BEFORE AND DURING PREGNANCY AND DURATION OF SECOND STAGE OF LABOR AMONG HISPANIC WOMEN

Introduction

The second stage of labor is defined as the period between complete dilation of the cervix and delivery of the fetus. In 1861, Hamilton first defined prolonged second stage of labor to be more than 120 minutes (1), and Emanuel Friedman in 1955-56 found the mean duration of this stage to be 57 minutes for nulliparous (2) and 18 minutes for multiparous women (3). The American College of Obstetricians and Gynecologists (ACOG) defines a prolonged second stage as lack of progress for 2 hours with, or 1 hour without, regional anesthesia in multiparous women and more than 3 hours with, or 2 hours without, regional anesthesia in nulliparous women (4).

A prolonged second stage of labor is an important labor outcome with incidence ranging from 23.6% (5) to 26.7% (6) in uncomplicated nulliparous term pregnancies. Prolonged second stage has been associated with adverse maternal outcomes such as increased rates of perineal trauma, episiotomy, chorioamnionitis, post partum hemorrhage and operative vaginal delivery in both nulliparous and multiparous women (7-11). Also, adverse fetal outcomes, including lower Apgar scores, meconium stained amniotic fluid, higher intensive care admission rates and longer hospital stay have been reported in multiparous women (10). Increased intracranial pressure (12, 13) and fetal acidosis (14) are also associated with prolonged second stage.

The use of epidural analgesia (8, 15-20) and nulliparity (8, 15, 16, 21-24) are known risk factors for prolonged second stage of labor. However, the association between physical activity and duration of labor is less clear. We believe that physical

activity by affecting body mass index (BMI) (25-27) and threshold endorphin levels (28) may affect duration of labor.

Studies regarding physical activity and duration of second stage of labor are sparse and conflicting. These studies have suggested that pelvic floor exercises (29), aerobic exercise (30), non endurance exercise (31) and more than 30 minutes of 3 - 6 metabolic equivalents (METS) per day (32)during pregnancy may reduce the second stage of labor. However, one study found an increased duration of labor among women who had an active lifestyle during pregnancy (33) whereas several other studies found no association between physical activity during pregnancy and duration of second stage of labor (34-36).

Puerto Rican women have a shorter mean duration of second stage (44.32 ±33.03 minutes) compared to white women (37) and a recent study found that Hispanic nulliparous women have second stages that are on average 6.8 minutes shorter (95% CI, 1.7-11.9 min) than white women (23). Important differences in the mean duration may exist between Hispanic subgroups but to date have not been evaluated. Hispanic ethnicity is a more important predictor of genetic ancestry than race (38). Those of Hispanic ethnicity are genetically different and may have a different relation between physical activity and duration of second stage of labor from other ethnic groups such as non-Hispanic Whites and Caucasians. The Hispanic population in the US is not only the largest minority group but also the fastest growing group with an increase from 12.5% in 2000 (39) to 16.3% in 2010 (40).Hispanics also have the highest fertility and birth rates (41) in the US. According to national surveys, Hispanic women report generally lower levels of recreational physical activity compared to non-Hispanic white women (42). In addition, Hispanic women have a higher risk for cesarean delivery (43, 44).Therefore, it

is imperative to evaluate the association of physical activity with duration of second stage in Hispanic women.

Most of the previous studies were population based cohorts with very small sample size and none were conducted in Hispanic populations. In addition these studies did not examine various types of physical activities such as occupational, sport, household and active living. Therefore, we examined the association between total physical activity during pre, early and mid-pregnancy and duration of second stage of labor in a prospective cohort of Hispanic prenatal care patients at Baystate Medical Center, Springfield, MA. Physical activity was measured with a previously validated modified version of the Kaiser Physical Activity Survey (45) adapted from the Baecke physical activity survey (46).

Physiological mechanism

The physiological mechanism by which physical activity may affect second stage duration is unclear; however, three possible mechanisms have been reported. These mechanisms relate to the impact of physical activity on muscular strength, the woman's BMI or pregnancy weight gain and activity-related release of endorphins. In terms of the first mechanism, it is known that delivery is faster when women bear down actively with their uterine contractions (47). Physical activity is known to strengthen the tone of muscles, including the perineal muscles involved during the second stage (48). Studies have suggested that strong pelvic muscles may prolong labor while others have suggested that it will help in rotating the fetal head and thus shorten the second stage (49, 50). A randomized controlled trial found that pelvic floor muscle training did not facilitate or obstruct labor (51).

In terms of the second mechanism, an active woman may have a lower BMI and gain less weight during pregnancy than an inactive woman. Previous studies have associated increased BMI with an increase in overall duration of labor but not specifically the duration of the second stage (26, 33). Increased BMI is associated with dystocia (25) leading to prolonged labor and the need for labor augmentation (26). Conversely, Buhimschi *et al*. found that intrauterine pressure during pushing was directly related to BMI suggesting that labor may be shorter with increasing BMI (52). Maternal weight gain during pregnancy has also been associated with prolonged second stage of labor (27). The conflicting evidence of the effect of higher BMI on prolonged second stage needs further exploration.

In terms of the third mechanism, stress hormones such as epinephrine, norepinephrine, adrenocorticotropic hormone, cortisol, prolactin and betaendorphins which peak at birth (53, 54) have been shown to facilitate labor (28). Evidence suggests that regular exercise increases the baseline beta endorphin level along with other stress hormones (55). Beta endorphins are opioid agonists released to reduce pain during exercise, but also act as a relaxing agent for muscles, thus facilitating labor (55)and potentially leading to a shorter second stage of labor. The link between physical activity and stress hormonal status may suggest a shorter and less painful second stage of labor with increasing physical activity(28, 53, 54). In terms of the timing of physical activity, pre-pregnancy activity has been strongly associated with physical activity during pregnancy and may contribute to the observed physiological effects during pregnancy.

In summary, although the three potential mechanisms may help to explain the association of physical activity and duration of second stage of labor, none of these have been clearly established. Of these mechanisms, the most likely may be the impact of

lesser physical activity on higher BMI and the direct association of higher BMI on prolonged second stage duration.

Epidemiologic Research

Epidemiologic research provides conflicting evidence on the association of physical activity with duration of second stage of labor. A recent meta-analytic review of 11 randomized and quasi randomized trials by Kramer *et al*. (2006) (56) concluded that the effect of aerobic exercise in pregnancy on labor duration should be studied with larger sample size. Kramer *et al*. also suggested better trials to predict its effect on labor as the prior trials had insufficient data to identify important risks or benefits of the exercise. An earlier meta-analytic review which included both observational studies and randomized trials consisting of 18 studies conducted before 1991 showed no association between aerobic exercise during pregnancy and length of labor (10.1± 4.5 hrs vs. 7.3 ± 1.2 hrs, p=0.14)(57). The majority of prior studies were of small size (sample size ranging from 20 to 2743) and quantified physical activity as exercise in general (30, 31, 35, 36, 58, 59), pelvic floor muscle exercise (29), active lifestyle (33) or moderate physical activity measured as 3-6 metabolic equivalents (METs) (32).

Previous studies that examined this association can be classified by their study designs as seven prospective cohort studies (31, 32, 34-36, 58), one retrospective cohort study (30) and two randomized control trials (29, 59). Of these ten studies, five studies showed no significant effect on duration of second stage of labor (29, 34-36, 59), four studies showed reduction in duration of second stage of labor (30-32, 58) and only one study showed an increase in duration of labor(33) with increased physical activity.

The most recent study by Meltzer *et al*. (2010) reported a reduction in duration of second stage for women who had ≥ 30 minutes of moderate physical activity per day

during their third trimester (32). A total of 44 Swiss women participated in this hospital based prospective study during their third trimester. The "resting metabolic rate" was measured using ventilated hood system and the "total energy expenditure" was measured for five days using a motor sensor called Actiheart. Metabolic equivalents (METs) were calculated using these two findings. A moderate physical activity was defined as METs between 3 and 6. They found a borderline significant decrease in duration of second stage of labor for active women (88 vs. 143 minutes, p=0.05). However, the study had limitations such as small sample size increasing the likelihood of type II error and a five day third trimester activity measurement increasing the likelihood of misclassification of exposure. This could have resulted in a biased effect estimate.

In the only large prospective cohort study, Magann *et al*. (n=2743) (34) used a previously validated self administered questionnaire for measuring physical activity as energy expenditure per day. Both nulliparous and multiparous women above 18 years of age completed the questionnaire between 16 to 18 weeks of gestation with the help of research midwives. The questionnaire evaluated daily activity and occupation, including a detailed job description and number of hours worked per week. A diary was completed daily with a detailed account of occupational and leisure time activity. Women were divided in five different categories according to the energy expenditure: Group 1, $\leq$2300 kcal/day; group 2, 2301 to 2500 kcal/day; group 3, 2501 to 2700 kcal/day; group 4 spent 2701 to 2900 kcal/day and group 5 >2900 kcal/day. There was no significant difference in the duration of the second stage of labor between the five groups overall or when stratified by parity. In a follow up study, Magann *et al*. (2002) (35) evaluated a sample of healthy low risk women (n=750), on active military duty from the previous study Magann *et al.* (1996) (34) thus making sure subjects were screened before enlistment for

major illness. This study sample was divided in four groups (*e.g.* no, light, moderate or heavy exercise) depending on frequency and gestational timings of mandatory, voluntary and aerobic exercise during pregnancy. Duration of second stage was not significantly different among the groups (No exercise = 48.1 ± 41.4, light =53.9 ± 45.4, moderate =65.7 ± 61.9 and heavy =52.6 ± 45.9; p =0.076). Neither of these studies included Hispanic women. In addition, the authors did not examine covariates such as analgesic drugs and episiotomy, which could have biased the results towards null. The study recorded physical activity after 16 to 18 weeks of gestation and only considered activity during pregnancy for analysis.

The only study which showed a positive association between physical activity and duration of labor was a prospective cohort of 24 women (33). Thirty women were interviewed during their third trimester and 24 eligible women were grouped as active (n=12) or sedentary (n=12). Active women were observed to have a longer duration of second stage compared to sedentary women (mean duration: 38.2 min vs. 19.9 min, p= 0.09), though, this difference was not statistically significant. The effect measure for predicting a difference in second stage duration could have been affected by small sample size (n=24). The women were classified into active and sedentary groups based on duration of aerobic exercise of 30 minutes at least three times a week. This could have led to a non-differential misclassification as the women in the sedentary group may have been exercising as a part of their job or household work, which may have further reduced the difference in duration among the two groups.

One of the prospective cohort studies that showed a reduction in duration of second stage of labor among exercising women included 100 nulliparous women(31). Fifty women were selected from a group of voluntary participants in a prenatal no-

endurance exercise program, and 50 non-exercising women were selected from the same private practice after being interviewed about their activity level. A questionnaire seeking pre-pregnancy activity levels sent to each participant during the last month of pregnancy showed no significant difference in their pre-pregnancy activity. However, the group involved in prenatal exercise had a shorter mean duration compared to the non-exercising group (1.33 hrs vs. 2.47 hrs, $p<0.001$). Women who chose to exercise during pregnancy could have been somehow different from those who chose not to exercise. For example, women in the exercise group may have been more concerned about their health and wellness and may have had a different biological response to labor compared to non-exercise group irrespective of their exercise program, resulting in confounding of relationship between exercise and second stage duration. Compared to exercising women (n=2), significantly more women in the non-exercising group (n=15) had epidural/general anesthesia, which is a known risk factor for prolonged second stage. The difference in duration was still significant after controlling for anesthesia.

In summary, the available epidemiological evidence on the association of physical activity and duration of second stage is conflicting and sparse. All the studies described above (29-36, 58, 59) were population based samples conducted on a largely white population. The results varied from no association to a positive or negative association of physical activity with duration of second stage of labor. Most of the studies had a small sample size and did not use a previously validated method for measuring physical activity except Magann *et al*. (32, 34, 35). However, Magann *et al* did not account for variables such as epidural analgesia, analgesic drugs and episiotomy. Moreover, pre-pregnancy physical activity was not used for association with duration of labor in any previous

studies. Many of the studies were subject to confounding because of self selection of the group.

Summary

Prolonged second stage of labor is associated with both maternal and fetal morbidity(7-14). Physical activity may affect the duration of labor via pathways pertaining to stress hormone levels (28, 53, 54), BMI (25, 26) and perineal muscle tone (48, 50, 51).

Women of Hispanic origin have a shorter mean duration of second stage compared to white women. The Hispanic population comprises the largest minority group in the United States representing 16.3% of the population(40) and has the highest fertility and birth rates (41). Therefore it is important to identify the association between physical activity and duration of second stage in Hispanic women. Epidemiologic studies of physical activity and second stage duration have had conflicting results and have been limited to a predominantly white population and have failed to assess the impact of pre-pregnancy activity. Prior prospective studies have been limited to small sample sizes with the exception of one (34) which did not examine the effect of variables such as epidural, episiotomy, gestational age and birth weight.

This study measured physical activity using a validated survey and evaluated the effect of pre, early and mid-pregnancy physical activity (household/caregiving, active living, sports/exercise and occupational) on duration of second stage of labor, in Hispanic women.

Specific Aims and Hypotheses

Specific Aim To evaluate the effect of physical activity during pregnancy and duration of second stage of labor among Hispanic women.

Hypothesis 1 Among Hispanic women, physical activity (categorized as household/caregiving, occupational, sports/exercise and active living) during **pre-pregnancy** is associated with shorter duration of second stage of labor.

Hypothesis 2 Among Hispanic women, physical activity (categorized as household/caregiving, occupational, sports/exercise and active living) during **early pregnancy** is associated with shorter duration of second stage of labor.

Hypothesis 3 Among Hispanic women, physical activity (categorized as household/caregiving, occupational, sports/exercise and active living) during **mid-pregnancy** is associated with shorter duration of second stage of labor.

Methods

Study Design and Population

We conducted a prospective cohort study using the data from the Latina Gestational Diabetes Mellitus Study (60) to evaluate the association between physical activity and duration of second stage of labor. The cohort was started in 2000 at Baystate Medical Center, a large public obstetrics and midwifery practice based in Western Massachusetts with an overall goal of studying the relationship between physical activity and gestational diabetes mellitus. Baystate Medical Center is a large tertiary care teaching hospital serving an ethnically and socioeconomically diverse population with approximately 4300 births annually. Among the pregnant population, 22% are Hispanic (mostly Puerto Rican origin), 11% are African American, 65% are non- Hispanic white and 2% are of other ethnicity.

Pregnant women who identified themselves as Hispanic were recruited during their first and second trimester, but before 24 weeks of gestation. Eligible subjects were interviewed twice during the study (Figure 1.1). We retrieved the duration of second

stage of labor along with other obstetric covariates like mode of delivery, analgesic usage, epidural anesthesia, BMI, episiotomy, gender of the infant, gestational age and parity from the electronic database of the hospital. Electronic data were merged with the cohort data using a unique identifier called “maternal medical record number”. Recruitment was conducted from September 2000 through December 2003 by bilingual interviewers after informing the patients about the aims of the study.

The participants signed an informed consent form approved by the Institutional Review Boards of University of Massachusetts, Amherst and Baystate Medical Center. Women who were non-Hispanic, had type 2 diabetes, hypertension, heart disease, chronic renal disease, were on medication known to adversely influence glucose tolerance (1%), had multiple gestation pregnancy (2%), were under 16 years or more than 40 years, or more than 24 weeks gestation or had previously participated in the study were excluded. A total of 2% refused to participate. A total of 1231 Hispanic women were enrolled in the Latina GDM cohort study.

Forceps and vacuum extraction are used when second stage is already prolonged, there is fetal distress or when second stage has to be shortened for maternal benefit because of her underlying medical problem. Cesarean section which is performed for the same reasons as forceps or vacuum extraction, does not provide an accurate second stage duration as the end point is never reached. Therefore, we considered only women with spontaneous vaginal deliveries for this study, thus excluding forceps, vacuum extraction and Cesarean section from the cohort. We excluded women who had no delivery information (did not deliver at Baystate or did not continue the pregnancy) (n=167), had preterm birth (n=129), spontaneous abortion (n=28), induced abortion (n=5), cesarean delivery (n=160) or a vacuum or forceps extraction (n=17) (Table 1.1).

Exposure Assessment

We assessed physical activity information on two separate occasions. The initial interview conducted between 18 to 20 weeks of gestation retrospectively collected physical activity information one year prior to pregnancy (pre-pregnancy) and early pregnancy (time from detection of pregnancy to 18-20 weeks of gestation). The second interview collected information about mid-pregnancy (period between first interview to 24-28 weeks) (see Figure 1.1). Participants who were not located for their second interview were contacted via telephone. The second interview was completed among 71% (n=710) of the participants. Those who did not complete their second interview were either not receiving primary prenatal care at the hospital or could not be located at clinic or contacted by telephone.

Physical activity was assessed via a modified version of the Kaiser Physical activity Survey (KPAS), adapted from the Baecke physical activity survey (46). The questionnaire was designed specially to assess physical activity in women. Women registered for prenatal care were approached regarding the study during their scheduled prenatal visit at the hospital. Bilingual interviewers enrolled the participants who completed this questionnaire consisting of four categories of physical activities namely 1) "Household/Caregiving" (11 items) which included child and elder care activities, meal preparation, cleaning, shopping, gardening and yard work; 2) "Occupational activities" (11 items) which included sitting, standing, walking, heavy lifting and sweating from exertion; 3) "Active living habits/leisure" (4 items) which included television, walking, bicycling to work or school; and 4) "Sports/Exercise" (15 items) which included questions about participation and sweating from exertion during sports and exercise.

The response in each category of activity was based on a 5 point Likert scale where 1 stands for never or none and 5 stands for always or more than once a week. Sports category questions were open ended and the responses to these questions were converted to a 5 point scale by multiplying the intensity of the activity by the duration of performance. Physical activity indices were created by adding the responses in each category and dividing by the number of questions in each category, thus a value ranging from 1 to 5 was generated for each category of physical activity. For example, if the sum of responses for household category was 44 for 11 different questions in the category, the household/ care-giving index would be 4. A total physical activity variable was created for pre, early and mid-pregnancy by combining the indices from the four different categories. The exposure data values of pre, early and mid-pregnancy along with total activity index for each period were further categorized in quartiles for analysis. However, the occupational activity was treated as three different categories instead of quartiles. The lowest category was unemployed with the other two categories being "below" or "above" than median of the total activity index.

Validity of Exposure Assessment

The instrument for exposure assessment was validated in a previous study (45) among 54 pregnant women from Baystate Medical Center using 7 days of accelerometer measurements. Comparisons with a pregnancy physical activity questionnaire (PPAQ) and the KPAS showed Spearmans correlations ranging from $r = 0.71$ for household/caregiving to $r = 0.84$ for sports/exercise. The validity of KPAS was also assessed by Ainsworth *et al*. using 50 non-pregnant women aged 20-60 years and administering the questionnaire one month apart (61). Intra-class correlations for 1-month test-retest reliability were very high with coefficients ranging from r = 0.79 to 0.91

($p<0.01$) for all KPAS activities. The correlations between KPAS and other direct and indirect methods among non-pregnant methods (VO2 peak, percent body fat) gave moderate results ranging from -0.3 to 0.76.

Outcome Assessment

Baystate Medical Center has an electronic database that stores the clinical information for each patient in a real time format. We retrieved the duration of second stage of labor from each participant. The duration of second stage was measured from complete cervical dilation (10 cm) to the time of fetal expulsion and was entered by the attending medical personnel (obstetrician, nurse or midwife) in the electronic database. The duration of labor in minutes was treated as a continuous variable. If the duration of second stage was entered as 0 min it was converted to 0.5 minutes. The recorded second stage duration was considered invalid if it was either less than 0.5 minutes or more than 10 hours and excluded from the analysis.

Validity of Outcome Assessment

The validity of electronic medical records as a source for duration of second stage has not been examined but prior studies have used duration as a continuous variable(29-31, 34, 58, 59). To reduce the risk of invalid values we excluded values less than a minute or more than 10 hours. Duration of second stage of labor was entered by the attending medical personnel and was abstracted from hospital records by an individual blinded to the physical activity levels of the participants.

Covariate Assessment

The major risk factors for prolonged second stage of labor are use of epidural analgesia (8, 15-20) and nulliparity (8, 15, 16, 21-24). Information about epidural analgesia and parity was retrieved from the electronic database and assessed as

dichotomous variables. The information on age and BMI retrieved from the electronic database was confirmed by comparing with self-reported data. Contradictory values of age and BMI were reexamined by retrieving the date of birth, weight and height of the subject from the electronic database.

Information about other important risk factors for duration of second stage of labor such as age (17, 62, 63), BMI (26, 33), weight gain during pregnancy, episiotomy (64), induction of labor, best clinical estimate of gestational age, analgesics (at least one of the following butorphanol tartarate, morphine sulfate, meperidine hydrochloride or fentanyl given within 8 hours of delivery) (19) and gender of the infant were retrieved from the electronic database of the hospital. Information about demographics and socioeconomic indicators such as maternal age, pregravid weight, height, total energy intake, substance abuse (*e.g*. smoking, alcohol and cocaine), education, income, access to prenatal care and insurance coverage was collected during the interviews.

Maternal nutrition also plays a crucial role in muscular strength and is also correlated with physical activity (65). Information about total energy intake, omega-3 fatty acids, saturated, monounsaturated and polyunsaturated fatty acids, cholesterol, dietary fiber, vitamin D, alpha-tocopherols and calcium were assessed in the Latina GDM cohort by administering a Food Frequency Questionnaire (65).

Data Analysis Plan

Univariate analysis

The distribution of physical activity indices (household/caregiving, sport/exercise, occupation, active living and total) for pre, early and mid-pregnancy are presented as mean, standard deviation, median and range (Table 1.3a). A comparison of pre, early and mid-pregnancy physical activity is presented as mean and standard deviation with a p

value from repeated measures ANOVA (Table 1.3b). The distribution of maternal and obstetrics covariates in the study sample is presented as number and percent (Table 1.2) along with the distribution of nutritional covariates as means and standard deviation (Table 1.5).

We used a directed acyclic graph (DAG)(66) to deduce the important covariates to be adjusted for during the analysis (Figure 1.2). DAGs visually depict our assumptions about causal relations between exposure, outcome and covariates. For example, parity affects duration of second stage directly therefore an *arc* connects the *parent* (parity) to the *child* (duration of second stage). Parity also affects duration of second stage indirectly via BMI and this path is called a *directed* or *causal* path i.e. a child (BMI) in the sequence is a parent in the next step, Parity→ BMI→Second stage. A *back-door* path from physical activity to duration of second stage is a path which starts with arc pointing towards physical activity i.e. Physical activity ← Parity → Duration of second stage. A *directed* graph that has all connections using *arcs* and if there are no closed loop of directed paths it will also be *acyclic*. A variable where two heads of arcs in a path meet is called a *collider*, *e.g.* Physical Activity/Gestational Age → Birth weight ← Smoking and Alcohol (Figure 1.2).

Assuming negligible uncontrolled confounding, all the important covariates were used for plotting the DAG. After deleting all the physical activity effects (arrows emanating from the exposure-physical activity) the rest of the *acyclic* pathways were analyzed for *unblocked* pathways from exposure (physical activity) to duration of second stage (exposure and outcome may be associated without the exposure effects). The '*minimally sufficient adjustment*' set of confounders was detected by using the backdoor

test and excluding the pathways with *colliders*. This minimally sufficient adjustment set included parity, BMI and maternal age.

Bivariate analysis

We assessed the individual effect of each covariate on duration of second stage through separate linear regression models. To evaluate the association of covariates with the duration of second stage, mean duration of second stage for each category of a covariate was compared to a referent group (Table 1.4). The associations between nutritional covariates and duration of second stage were similarly evaluated using linear regression (Table 1.5). Total energy intake is always related with disease risk because of the association of physical activity and disease risk. Intake of micronutrients is also correlated with total energy intake (67). Therefore, we also adjusted for total energy intake to examine any change in the association between nutritional covariates and duration of second stage (Table 1.5).

We calculated the unadjusted means of duration of second stage and tested for trends across categories of physical activity (pre, early and mid-pregnancy) using linear regression (Table 1.6, 1.7 and 1.8). The means of the upper three quartiles were compared to the least square means of the reference first quartile (least active) using Scheffe's method for multiple comparisons in a linear regression.

Multivariable analysis

We used multiple linear regression to model the relationship between physical activity and duration of second stage of labor, adjusting for variables found to be significant in the bivariate analysis (Table 1.4 and 1.5) and variables from the minimally sufficient adjustment set (age, parity and BMI) as shown in DAG (Figure 1.2). This minimally sufficient adjustment set was included in all models. Simulation studies have

found that use of p<0.05 for selection of confounding variables in a statistical model can lead to deletion of significant confounders (false negatives). Therefore we excluded other covariates using backward elimination with a less conservative $p < 0.2$ (68, 69). The remaining covariates in the model were kept only if they change the effect estimate by more than 10% (69). The covariates that significantly affected the effect estimate other than maternal age, parity and BMI were infant birth weight, epidural, episiotomy, smoking, infant gender and intravenous analgesics. Other obstetrics and nutritional covariates (Table 1.4 and Table 1.5) were not significant confounders. We calculated least square means for the quartiles of each category of physical activity (Table 1.6, 1.7 and 1.8).We also assessed potential dose response relationships at p< 0.05 for any of the activity indices found to have a significant difference in the least square means.

Parity and infant birth weight lead to structural changes in the uterus along with an increase in maternal and neonatal complications, thus significantly altering the duration of second stage of labor. The physiological changes associated with parity and higher birth weight may alter the association between activity and second stage duration. We believe that the association between physical activity and duration of second stage would be stronger in nulliparous women and heavier infants. We therefore assessed the effect modification by parity and infant birth weight for activity indices which were significantly associated with the duration of second stage of labor.

Sample size and Power

To detect a mean difference of 10 min at standard deviation of 35 minutes with each quartile consisting of 201 women at alpha of 0.05, we had a power of 82% (Table 1.11).

Missing Data Analysis

Out of the 1231 participants of the Latina GDM study, we excluded preterm births (n=129), spontaneous abortions (n=28), induced abortions (n=5), cesarean section (n=160), a vacuum or forceps extraction (n=17) and 167 had no delivery information (did not continue pregnancy or did not deliver at Baystate Medical Center). Characteristics of women included in the study (n=725) were compared to those who had no delivery information (n=167) either because of discontinuation of pregnancy or delivery at a different hospital to assess significant differences among the important predictors for duration of labor (Table 1.9). Student's t test and chi square analysis were used as appropriate to evaluate the differences in various continuous and categorical variables. A similar comparison of physical activity indices between those in the study sample and those with no delivery information was conducted (Table 1.10). Finally, almost 29% of the sample was missing information on mid-pregnancy physical activity due to failure to complete the second interview and therefore were not included in the analysis with mid-pregnancy activity as the primary exposure variable. Comparison of maternal and obstetrics characteristics was conducted between these two groups using Student's t test and chi-squared test.

Results

A total of 725 (58.9%) women with singleton, normal vaginal deliveries were included in the final analysis. The study population was predominantly young, multiparous, and had less than a high school education (Table 1.2). The majority of participants had a family history of diabetes mellitus and almost half were overweight or obese. Nearly half of the participants received epidural analgesia. The mean duration of second stage of labor was 34.3 minutes (SD=42.02) with a range from 0.5 to 312

minutes. The distribution of quartiles of physical activity indices for each pregnancy activity category showed a significant decrease (P value from Repeated measures ANOVA < 0.0001) in physical activity starting from pre to mid-pregnancy (Table 1.3a and 1.3b).Maternal age, BMI, parity, epidural, episiotomy, analgesics, gestational age and birth weight were significantly associated with duration of second stage in an unadjusted analysis comparing least squared means (Table 1.4). Through evaluation of nutritional covariates using similar linear regression method, revealed that caffeine had a significant negative association with duration of second stage of labor (β estimate= - 0.06, *P*=0.03) (Table 1.5). This association remained significant after controlling for total energy intake.

For pre-pregnancy activity, in unadjusted analyses we observed that mean duration of second stage of labor differed significantly across quartiles of household/caregiving activity (Table 1.6). Women with the highest levels of household/caregiving activity had a significantly shorter mean duration compared to women in the lowest quartile of household/caregiving activity (29.1 vs.46.4 min, P_{trend}<0.0001). However, this finding was no longer statistically significant after adjusting for parity, BMI, infant birth weight, maternal age, cigarette smoking, gender of the infant, epidural, episiotomy and analgesic drugs (43.4 vs. 40.7 min, P_{trend}=0.76) (Table 1.6). The mean duration of labor also did not differ according to quartiles of pre-pregnancy sports/exercise, occupational and active living habits.

For early pregnancy activity, in unadjusted analyses, mean duration of second stage of labor differed across categories of household/caregiving, occupational and total activities (Table 1.7). Similar to the pre-pregnancy period, women with higher household activity had significantly shorter mean duration compared to women in the lowest quartile of household/caregiving activity (22.7 vs.43.9 min, p<0.0001), but this finding

was attenuated and no longer statistically significant in multivariable analyses (36.9 vs. 38.6 min, P_{trend}=0.85). Unlike the pre-pregnancy period, employed women with the highest levels of occupational activity in early pregnancy had a significantly longer mean duration compared to unemployed women (42.1 vs. 30.6 min, P_{trend}=0.005). This finding, however, was also attenuated and no longer statistically significant in multivariable analyses (44.2 vs. 36.1 min, P_{trend}=0.06). Increasing levels of total early pregnancy activity were inversely associated (P_{trend}=0.03) with duration of second stage but this trend did not remain significant (P_{trend}=0.38) in multivariable analysis. The mean duration of labor also did not differ according to quartiles of early pregnancy sports/exercise or active living habits.

For mid-pregnancy activity, we again observed that mean duration of second stage of labor differed significantly across categories of household/caregiving activity (30.3 vs. 43.4 min, *P*=0.03) in the unadjusted model but was no longer significant in multivariable analyses (Table 1.8). Duration of labor did not differ, however, according to any other domain of mid-pregnancy activity.

We assessed effect modification by parity and infant birth weight. These findings were not statistically significant at *P*=0.1. Our primary analysis excluded women with forceps and vacuum extraction deliveries as prolonged second stage of labor is an indication for these procedures. However, we performed a sub-analysis including these women (n=17). Results were virtually unchanged.

Comparison of maternal and obstetrics covariates between those included in the study (n=725) and those who did not have delivery information (n=167) showed no significant difference between these two groups. However, those who had no delivery information and therefore were excluded were more likely to be smokers (*P*=0.02) (Table

1.9). A similar comparison of physical activity indices between these two groups showed no significant difference in the amount of physical activity except for mid-pregnancy household activity (Table 1.10). Women missing delivery information were more active at home during mid-pregnancy compared to those included in the study (P=0.03).

Comparison of maternal and obstetrics characteristics was conducted between those with missing information on mid-pregnancy physical activity due to failure to complete the second interview (29%) and those included in the study. Participants missing this information did not differ statistically from those with mid-pregnancy information in terms of epidural use, age, smoking, BMI, labor induction and total pre-pregnancy activity but were more likely to be parous, and to receive intravenous analgesics and were less active during early pregnancy (results not presented).

Discussion

In this prospective study of Hispanic women, we found no association between pre, early and mid-pregnancy household/caregiving, sports/exercise, occupational and active living habits and duration of second stage of labor. We observed a trend of decreased duration of second stage of labor among women with increasing levels of household/caregiving activity in pre, early, and mid-pregnancy as well as with increasing levels of total activity in mid-pregnancy, however, these findings were attenuated after adjusting for medical and obstetric risk factors. We observed a longer duration of second stage of labor among women with the highest levels of occupational activity in early pregnancy as compared to unemployed women which was also attenuated after adjusting for other risk factors.

Our results in Hispanic women are similar to other recent studies which showed no association between maternal physical activity and duration of second stage of labor.

In the largest prospective cohort study to date, Magann *et al*. observed no association between energy expenditure and duration of second stage of labor (34). Analysis of a subset of this sample consisting of 750 low risk women, attending a prenatal clinic and leading an active lifestyle(35) found that duration of second stage was not significantly different among groups with no, light, moderate and heavy exercise. Salvesen *et al*.(29) found no difference in second stage of labor among 301 nulliparous women randomly allocated to a pelvic floor muscle training program or a control group. Similarly in our study, we found that second stage of labor was not significantly different according to levels of sports/exercise in pre, early, and mid-pregnancy.

The most recent study of 44 Swiss women by Meltzer *et al*. (2010) reported a reduction in duration of second stage for women who had ≥ 30 minutes of moderate physical activity per day during their third trimester (32). They found a borderline significant decrease in duration of second stage of labor for active women (88 vs. 143 minutes, P=0.05). Our unadjusted analysis of household activity showed similar significant reduction in duration of second stage which later attenuated after adjusting for medical and obstetric risk factors

Our study is subject to several limitations. Error associated with self-reported physical activity was minimized by administration of previously validated questionnaires by bilingual interviewers who used memory cues to elicit accurate information. The self reported nature of the questionnaire could have lead to non differential misclassification biasing the association towards the null. However, previous studies have shown that the questionnaire is a reliable and valid indicator of true physical activity leading us to believe that this bias is minimal (45). In addition, the prospective nature of the study design ensured that physical activity was reported prior to delivery, and therefore not

influenced by duration of labor. Also, the collection of duration data was not in any way affected by the exposure as the duration was recorded by a health personnel unaware of the physical activity levels of the woman.

It should also be noted that we excluded women who had a cesarean section during the second stage of labor (n=106) as it is difficult to define the end point of the second stage in this situation. This exclusion prevented us from evaluating the association between activity and duration of second stage. Assuming that women in this excluded sample are more likely to have longer duration of second stage and are less physically active we may have underestimated our effect estimate.

Finally, 29% of the sample was missing information on mid-pregnancy physical activity and therefore were not included in the mid-pregnancy activity analysis. Participants missing this information were more likely to be parous, receive intravenous analgesics and were less active during early pregnancy. To the extent that these factors were associated with duration of labor, this missing data could have biased our findings. However, the fact that our findings for mid-pregnancy were not substantively different from our findings for pre and early pregnancy reduces this concern.

Approximately 13.6% of participants were excluded from the analysis because they delivered elsewhere. This figure is higher than prior pregnancy cohorts of predominantly non-Hispanic white populations, and is likely reflective of the circular migratory patterns of women of Puerto Rican or Dominican descent (70). However, women who delivered elsewhere did not differ significantly from women who delivered at Baystate in terms of their sociodemographic characteristics, clinical characteristics, or physical activity.

There is also a possibility of residual confounding due to erroneous measurement of the covariates such as age and parity. Although we tried to include the known potential confounders in our analysis, active women are intrinsically different from less active women. This difference can be attributed to some unmeasured confounding which we could not account for. However, we consider such confounding to be minimal and absence of its adjustment would have a negligible influence on our effect estimates.

The predominantly Puerto Rican participants in the Latina Gestational Diabetes study, self enrolled for the study and attended the prenatal care clinics in a tertiary care hospital; study participants may have been more health-conscious than the general population of Hispanic women, and therefore more likely to engage in sports and exercise, though household and caregiving or occupational activities would not be expected to similarly vary. Although we believed that there might be an effect modification by ethnicity we found our results to be consistent with most of previous studies conducted in non-Hispanic women. Nevertheless it is not clear that the association between physical activity and duration of second stage would differ among various Hispanic subgroups.

In summary, in this prospective study, after adjusting for risk factors associated with duration of labor, pre, early and mid-pregnancy household/caregiving, sports/exercise, occupational, and active living activities were not associated with duration of second stage of labor in this Hispanic population. These findings confirm are in agreement with prior literature suggesting the absence of an association between physical activity and duration of labor in non-Hispanics.

Significance

To date, no study has evaluated the effect of pre, early and mid-pregnancy physical activity on duration of second stage of labor, especially among Hispanic women who represent 16% of the US population. It is important to know that a modifiable risk factor such as physical activity does not necessarily effect the duration of second stage which if prolonged is associated with various morbidities.

Human Subjects

The Latina GDM Study was approved by the Institutional Review Board of University of Massachusetts at Amherst and Baystate Medical Center. All participants were required to sign an informed consent indicating that they understood that they were under no obligation to participate, that their medical care would not differ based on participation, and that they could withdraw at any time.

Every effort was made to ensure that confidential information remains secure. Study personnel are trained in privacy protocols and completed questionnaires and medical records forms will be kept under lock and key. Computer files were kept on a secure server which was password protected, with only study personnel able to access the files.

There were no known risks to participants and there was no breach in confidentiality. There were no known benefits to participation with the exception of advancing science in a population of women underrepresented in previous research.

Permission to Access Data

Professor Dr. Lisa Chasan-Taber granted permission to access relevant data from her grant funded Latina Gestational Diabetes Mellitus study for the dissertation topic,

"Physical activity before and during pregnancy and duration of second stage of labor among Hispanic women" on 2nd November 2007.

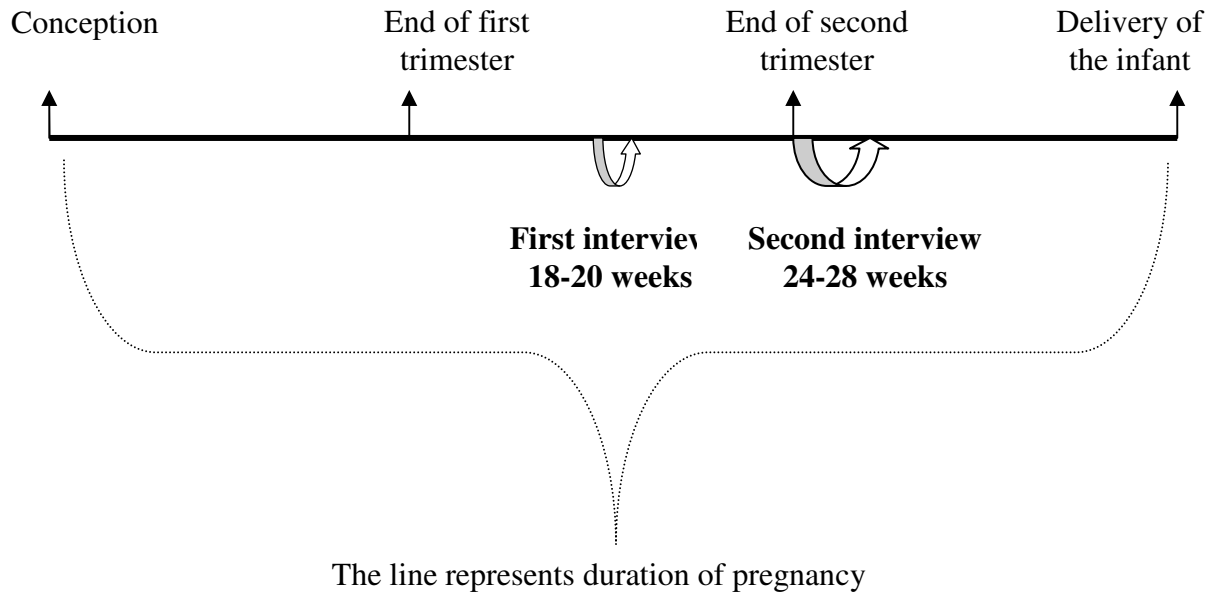


Figure 1.1 Time line for interview in the Latina Gestational Diabetes Mellitus (GDM) Study 2000-2003 to measure physical activity and other variables

Table 1.1 Selection of study sample from Latina GDM cohort 2000-2003, to evaluate the association between physical activity and duration of second stage of labor.

Characteristics	N	%
Total enrollment	1231	100
Excluded from Analysis		
No delivery information	167	13.5
Preterm Births	129	10.5
Cesarean Delivery	160	13
Vacuum or Forceps Delivery	17	1.4
Spontaneous Abortions	28	2.3
Induced Abortions	5	0.4
Total in Analysis	725	58.9

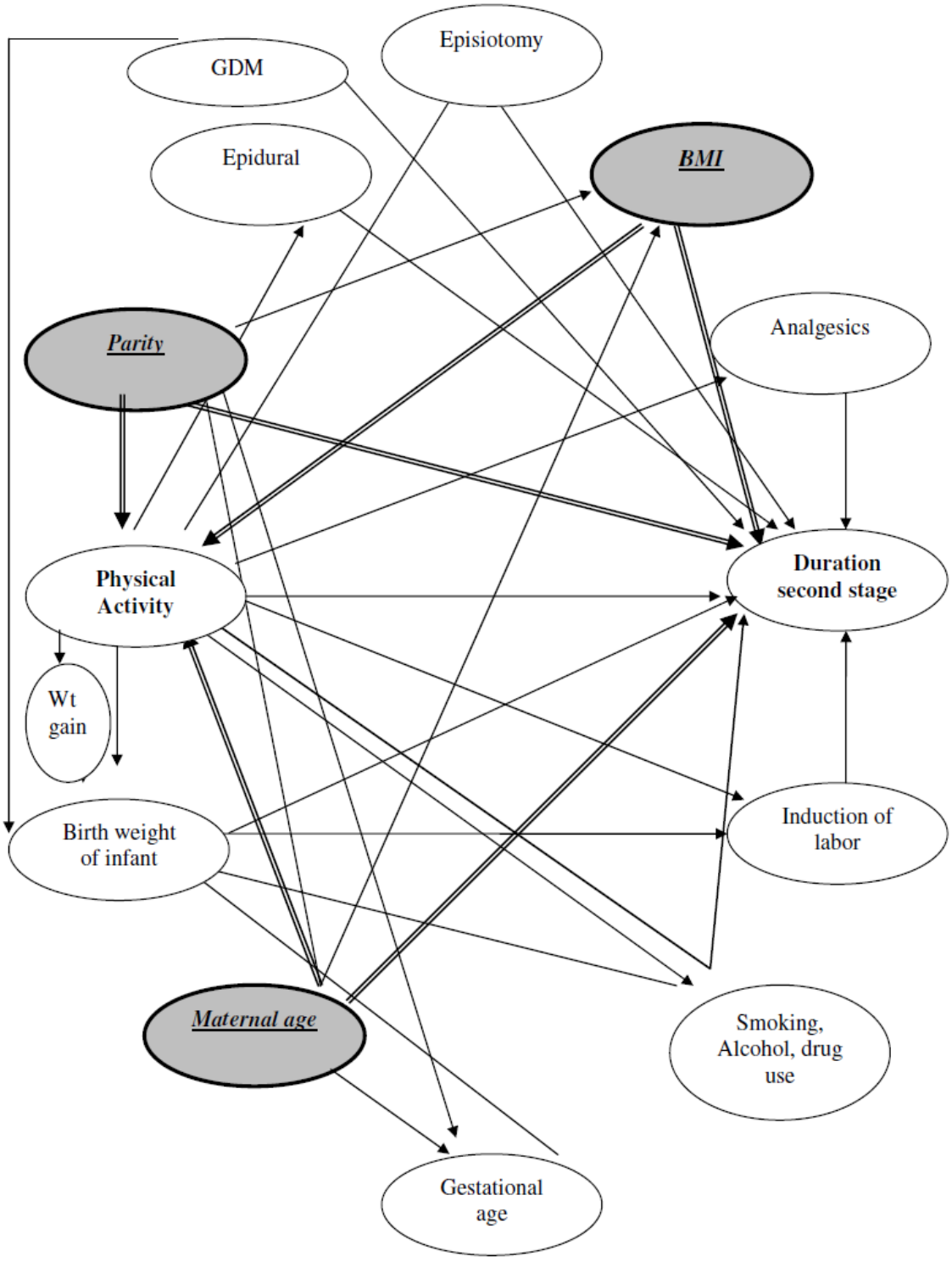


Figure 1.2 Directed Acyclic Graph to detect the minimally sufficient adjustment set for evaluating the association of physical activity with second stage of labor

Table 1.2 Distribution of covariates in study evaluating association of physical activity with duration of second stage (n=725)

Characteristics	**n (%)**
Maternal age (years)	
15-19	251 (34.6)
20-24	292 (40.3)
25-29	123 (17.0)
30-40	59 (8.1)
Parity	
0	279 (38.6)
≥1	444 (61.4)
BMI (kg/m^2)	
<20	103 (14.5)
20-24.9	271 (38.2)
25-29.9	178 (25.1)
30+	158 (22.2)
Birth weight (gms)	
<2500	35 (4.9)
≥2500 and <4000	637 (89.2)
≥ 4000	42 (5.9)
Smoking during pregnancy	
Yes	129 (19.4)
No	536 (80.6)
Alcohol (≥1 times per week during pregnancy)	
Yes	14 (2.1)
No	654 (97.9)
Any illicit drug use during pregnancy	
Yes	39 (5.8)
No	629 (94.2)
Annual household income ($)	
≤ 15,000	235 (59.3)
15,000-30,000	122 (30.8)
>30,000	39 (9.9)
Education	
Less than high school	360 (55.6)
High school/trade or tech school	208 (32.2)
Undergrad/grad College	79 (12.2)
Epidural	
Yes	296 (49.7)
No	300 (50.3)
Intravenous analgesics *	
Yes	88 (14.8)
No	508 (85.2)
Family history of diabetes mellitus	
Yes	434 (63.9)
No	245 (36.1)
Induction of labor	

Yes	345 (58.1)
No	249 (41.9)

* Atleast one of butorphanol tartarate, morphine sulfate, meperidine hydrochloride or fentanyl given < 8 hours of delivery

Table 1.3a Distribution of the Quartiles of Physical Activity Indices in the study evaluating association of physical activity with duration of second stage of labor: Latina GDM Study 200-2003

Activity indices	Pre-pregnancy Activity Index			Early Pregnancy Activity Index			Mid-Pregnancy Activity Index		
	n (%)	Range	Median	n (%)	Range	Median	n (%)	Range	Median
household/caregiving	670 (92.4)			660 (91)			494 (68.1)		
1st quartile	181	1 - 2.11	1.88	196	1 - 1.88	1.66	113	1 - 1.88	1.55
2nd quartile	148	2.11 - 2.55	2.33	121	1.88 - 2.33	2.11	138	1.88 - 2.22	2
3rd quartile	191	2.55 - 2.88	2.66	189	2.33 - 2.66	2.44	139	2.22 - 2.66	2.44
4th quartile	150	2.88 - 4.44	3.22	154	2.66 - 3.66	3	104	2.66-3.77	2.88
sport/exercise	644 (88.8)			638 (88)			491 (67.7)		
1st quartile	154	1 - 1.5	1.25	151	1 - 1.25	1	96	1 - 1.25	1
2nd quartile	175	1.5 - 2	1.5	168	1.25 - 1.29	1.25	118	1.25 - 1.5	1.25
3rd quartile	151	2 - 3.5	2.75	147	1.29 - 1.75	1.5	143	1.5 - 1.75	1.5
4th quartile	164	3.5 - 5	4	172	1.75 - 4.5	2.5	134	1.75 - 4.5	2.5
occupation	650 (89.6)			646 (89.1)			486 (67)		
1st quartile	172	1 - 1.0	1	NA	NA	NA	NA	NA	NA
2nd quartile	145	1.0 - 2.57	2	347	1 - 1.0	1	288	1 - 1.0	1
3rd quartile	182	2.57 - 3.85	3	146	1 - 2.71	2.28	73	1- 2.57	2.28
4th quartile	151	3.85 - 5	3.85	153	2.71 - 4.83	3.28	125	2.57 - 4.28	3.14
active living habits	650 (89.6)			641 (88.4)			494 (68.1)		
1st quartile	159	1 - 2.25	1.5	151	1 - 1.75	1.25	120	1 - 2.0	1.5
2nd quartile	136	2.25 - 2.75	2.5	203	1.75 - 2.25	2	92	2 - 2.5	2
3rd quartile	208	2.75 - 3.25	3	127	2.25 - 2.75	2.5	127	2.5 - 3	2.66
4th quartile	147	3.75 - 5	3.75	160	2.75 - 4.5	3.25	155	3 - 4.66	3.25
total activity	630 (86.9)			626 (86)			481 (66.4)		
1st quartile	160	5.11 - 8.83	7.92	167	4 - 7.46	6.9	122	4 - 7.5	6.74
2nd quartile	163	8.83 - 10.08	9.55	167	7.46 - 8.51	8.05	126	7.5 - 8.5	8.07
3rd quartile	151	10.08 - 11.39	10.75	137	8.51 - 9.85	9.17	120	8.5 - 9.68	9.18
4th quartile	156	11.39 - 16.68	12.46	155	9.85 - 15.08	10.72	113	9.68 - 14.84	10.59

Table 1.3b Comparison of pre, early and mid-pregnancy physical activity indices using Repeated measures ANOVA.

	Pre-Pregnancy	Early Pregnancy	Mid-Pregnancy	P-value*
Household/Caregiving	2.5 ± 0.57	2.28 ± 0.57	2.24 ± 0.55	<0.0001
Sports/Exercise	2.39 ± 1.18	1.62 ± 0.76	1.63 ± 0.71	<0.0001
Occupational	2.45 ± 1.09	1.85 ± 1.03	1.73 ± 0.97	<0.0001
Active Living	2.7 ± 0.85	2.28 ± 0.78	2.45 ± 0.74	<0.0001
Total Activity	10.14 ± 1.92	8.64 ± 1.68	8.62 ± 1.68	<0.0001

* Repeated Measures ANOVA

Table 1.4 Unadjusted Means of duration of second stage of labor for each category of covariates

Covariates	n	Pr>F Model	Means	P Value $
Age (Years)	725	**<0.0001**		
15-19			46.90	Ref
20-24			31.68	**<.0001**
25-29			19.83	**<.0001**
30-40			27.28	**0.00**
BMI (kg/m2)	710	**0.01**		
20-24.99			37.79	Ref
25-29.99			31.39	0.11
30+			26.35	**0.01**
<20			40.97	0.51
Parity	723	**<0.0001**		
Nulliparous			55.15	Ref
Multiparous			21.23	**<0.0001**
Education	647	0.47		
High /Trade /Tech School			38.29	Ref
Less than High School			34.63	0.32
Undergrad/grad College			30.46	0.16
Income ($)	396	0.64		
15,000- 30,000			34.61	Ref
≤ 15,000			28.94	0.18
>30,000			37.44	0.68
Smoking during Pregnancy	665	**0.06**		
No			36.45	Ref
Yes			28.76	0.06
Alcohol during Pregnancy	668	0.99		
No			34.87	Ref
Yes			34.85	0.99
Epidural	653	**<0.0001**		
No			28.51	Ref
Yes			44.07	**<0.0001**
Episiotomy	653	**<0.0001**		
No			33.83	Ref
Yes			75.97	**<0.0001**
Analgesic*	653	**0.01**		
No			38.17	Ref
Yes			25.05	**0.01**
Gender of infant	499	0.53		
Female			38.55	Ref
Male			36.60	0.53
Gestational age (weeks)	644	**0.00**		
37 - 39			31.33	Ref
> 40			42.91	**0.00**
< 37			25.03	0.28
Birth weight (g)	653	**<.0001**		
2500-4000			34.84	Ref
>4000			60.86	**0.00**
<2500			22.32	**0.03**
Induction of labor	648	0.81		
No			35.73	Ref
Yes			36.57	0.81

* - At least one of the four drugs butorphonal, tartarate, morphine sulfate, meperidine hydrochloride of fentanyl given 8 hours of delivery, $ p value for H0: LSMean(i)=LSMean(j)

Table 1.5 Distribution of nutrition covariates and their association with duration of second stage of labor: Latina GDM cohort study 2000-2003.

Nutrition Covariates	Mean ± S.D	Unadjusted		Adjusted for Total Energy	
		Beta estimate	*P value	Beta estimate	*P value
Total Energy Intake (kcal)	2838.54 ± 1291.87	-0.0003	0.82	-	-
Omega -3 (g)	1.84 ± 0.98	-0.41	0.84	0.02	0.99
Saturated Fatty Acids (g)	35.56 ± 18.16	0.009	0.3	0.24	0.43
Monounsaturated Fatty Acids(g)	33.55 ± 17.28	-0.0004	0.99	0.27	0.49
Polyunsaturated Fatty Acids (g)	28.68 ± 15.46	-0.014	0.915	0.07	0.81
Cholesterol (mg)	328.26 ± 159.71	0.004	0.74	0.01	0.37
Caffeine (mg)	49.88 ± 65.64	**-0.06**	**0.037**	**-0.06**	**0.034**
Dietary Fiber (g)	20.77 ± 11.96	-0.10	0.53	-0.21	0.45
Vitamin D (mcg)	8.07 ± 4.91	0.32	0.43	0.60	0.25
Alpha-Tocopherol Equivalents (mg)	20.75 ± 13.33	0.04	0.77	0.14	0.53
Calcium (mg)	1202.33 ± 656.41	0.001	0.62	0.004	0.33
Magnesium (mg)	376.57 ± 182.69	-0.001	0.89	0.003	0.89

A total of 456 out of 725 had complete and valid dietary information, *P value from linear regression model

Table 1.6 Unadjusted and adjusted means according to pre-pregnancy activity domains and duration of second stage of labor (n=725); Latina GDM study 2000-2003.

Activity indices	Unadjusted	Adjusted[$]
	mean (min)	mean (min)
Household/caregiving		
1st quartile[*]	46.4	40.7
2nd quartile	36.8	43.9
3rd quartile	26.5	41.0
4th quartile	29.1	43.4
P_{trend}	<0.0001	0.76
Sports/exercise		
1st quartile	33.1	46.0
2nd quartile	30.8	40.2
3rd quartile	39.5	42.3
4th quartile	34.9	39.1
P_{trend}	0.3	0.41
Occupational		
Unemployed	33.8	47.6
Below the median	34.4	40.5
Above the median	35.8	41.9
P_{trend}	0.62	0.23
Active living habits		
1st quartile	32.9	43.3
2nd quartile	29.9	36.9
3rd quartile	35.5	41.4
4th quartile	40.2	51.9
P_{trend}	0.11	0.22
Total activity		
1st quartile	43.5	47.8
2nd quartile	30.7	35.6
3rd quartile	28.5	35.6
4th quartile	36.5	43.7
P_{trend}	0.14	0.49

$ = Adjusted for parity, body mass index at first visit, infants birth weight, episiotomy, epidural, age, smoking, gender of the infant and intravenous analgesics.
[*]1st quartile represent the least active group whereas 4th quartile represents the most active group
P trend: P for trend calculated across the median of the quartile of each activity index

Table 1.7 Comparison of means for unadjusted and adjusted association between early pregnancy physical activity indices and duration of second stage of labor (n=725).

Activity indices	Unadjusted mean (min)	Adjusted[$] mean (min)
Household/caregiving		
1st quartile[*]	43.9	38.6
2nd quartile	37.4	40.8
3rd quartile	32.3	41.8
4th quartile	22.7	36.9
P_{trend}	<0.0001	0.85
Sports/exercise		
1st quartile	34.4	41.5
2nd quartile	37.1	40.8
3rd quartile	27.7	33.1
4th quartile	38.4	41.3
P_{trend}	0.36	0.85
Occupational		
Unemployed	30.6	36.1
Below the median	36.3	40.2
Above the median	42.1	44.2
P_{trend}	0.0047	0.06
Active living habits		
1st quartile	34.4	38.1
2nd quartile	34.7	38.9
3rd quartile	33.7	36.4
4th quartile	35.6	41.0
P_{trend}	0.83	0.65
Total activity		
1st quartile	40.6	37.3
2nd quartile	36.5	41.0
3rd quartile	29.9	36.2
4th quartile	31.6	43.3
P_{trend}	0.03	0.38

$ =Adjusted for parity, body mass index at first visit, infants birth weight, episiotomy, epidural , age, smoking, gender of the infant and intravenous analgesics.

[*] 1st quartile represent the least active group whereas 4th quartile represents the most active group

Ptrend: P for trend calculated across the median of the quartile of each activity index

Table 1.8 Comparison of means for unadjusted and adjusted association between mid-pregnancy physical activity indices and duration of second stage of labor (n=725).

Activity indices	Unadjusted mean (min)	Adjusted[$] mean (min)
Household/caregiving		
1st quartile[*]	43.4	35.1
2nd quartile	39.9	42.1
3rd quartile	33.2	39.7
4th quartile	30.3	40.1
P_{trend}	0.01	0.63
Sports/exercise		
1st quartile	32.8	34.5
2nd quartile	38.6	43.3
3rd quartile	33.1	37.2
4th quartile	42.1	40.7
P_{trend}	0.14	0.58
Occupational		
Unemployed	34.9	39.3
Below the median	45.7	44.2
Above the median	36.7	37.7
P_{trend}	0.42	0.92
Active living habits		
1st quartile	37.2	43.8
2nd quartile	38.8	38.9
3rd quartile	36.2	41.4
4th quartile	35.9	35.3
P_{trend}	0.71	0.19
Total activity		
1st quartile	38.3	38.3
2nd quartile	41	41.7
3rd quartile	35.2	38.6
4th quartile	33.2	39.4
P_{trend}	0.27	0.98

$ Adjusted for parity, body mass index at first visit, infants birth weight, episiotomy, epidural, age, smoking, gender of the infant and intravenous analgesics.
[*] 1st quartile represent the least active group whereas 4th quartile represents the most active group
Ptrend = P for trend calculated across the median of the quartile of each activity index

Table 1.9 Comparison of distribution of covariates between study sample and subjects with no delivery information.

	Study Sample 725 n (%)	**Missing 167 n (%)**	**χ 2, P value**
Parity			
0	279 (38.6)	41 (36.6)	0.69
≥1	444 (61.4)	71 (63.4)	
missing	2	55	
BMI (kg/m2)			
<20	103 (14.5)	21 (14.5)	0.75
20-24.99	271 (38.2)	56 (38.6)	
25-29.99	178 (25.2)	41 (28.3)	
30+	158 (22.1)	27 (18.6)	
missing	15	22	
Maternal age (years)			
15-19	251 (34.6)	58 (34.7)	0.53
20-24	292 (40.3)	59 (35.3)	
25-29	123 (16.9)	35 (20.9)	
30-40	59 (8.2)	15 (9.1)	
Smoking during pregnancy			
Yes	129 (19.4)	41 (27.7)	0.02
No	536 (80.6)	107 (72.3)	
Missing	60	19	
Alcohol (>=1 times per week)			
Yes	14 (2.1)	0	0.07
No	654 (97.9)	148 (100)	
Missing	57	19	
Any Illicit drug use during pregnancy			
Yes	39 (5.8)	8 (5.4)	0.84
No	629 (94.2)	140 (94.6)	
Missing	57	19	
Annual Income ($)			
≤ $15,000	235 (59.3)	42 (50.6)	0.32
15,000 to 30,000	122 (30.8)	30 (36.2)	
>30,000	39 (9.9)	11 (13.2)	
Missing	329	84	
Education			
less than HS	360 (55.6)	74 (54.4)	0.93
High/trade/tech school	208 (32.2)	46 (33.8)	
undergrad/grad College	79 (12.2)	16 (11.7)	
Missing	78	31	
Family history of Diabetes mellitus			
Yes	434 (63.91)	93 (66.4)	0.57
No	245 (36.1)	47 (33.56)	
Missing	46	27	

Table 1.10 Comparison of physical activity indices of study sample and subjects with no delivery information.

Activity indices as continuous variable	Study population (n=725)		No Delivery Information (n=167)		P value
	Mean ± SD	% missing	Mean ± SD	% missing	
Pre -pregnancy activity					
household/caregiving	2.5 ± 0.57	7.58	2.46 ± 0.56	9.58	0.40
sport/exercise	2.39 ± 1.18	11.17	2.6 ± 1.27	8.04	0.06
occupation	2.45 ± 1.09	10.34	2.37 ± 1.12	13.70	0.42
active living habits	2.7 ± 0.85	10.34	2.83 ± 0.83	15.56	0.10
total activity	10.14 ± 1.92	13.10	10.31 ± 1.82	17.96	0.35
Early pregnancy activity					
household/caregiving	2.28 ± 0.57	8.96	2.34 ± 0.56	8.38	0.24
sport/exercise	1.62 ± 0.76	12.00	1.66 ± 0.84	11.37	0.54
occupation	1.85 ± 1.03	10.89	1.88 ± 1.07	11.37	0.77
active living habits	2.28 ± 0.78	11.58	2.35 ± 0.79	10.77	0.33
total activity	8.64 ± 1.68	13.65	8.87 ± 1.70	13.17	0.15
Mid-pregnancy activity					
household/caregiving	2.24 ± 0.55	31.86	2.4 ± 0.59	58.68	**0.03**
sport/exercise	1.63 ± 0.71	32.27	1.75 ± 0.83	59.28	0.19
occupation	1.73 ± 0.97	32.96	1.63 ± 0.97	59.88	0.41
active living habits	2.45 ± 0.74	31.86	2.55 ± 0.76	58.68	0.29
total activity	8.62 ± 1.68	33.65	9.02 ± 1.92	60.47	0.08

Table 1.11 The power to detect a mean difference between duration of second stage among two physical activity groups of sample size 201 each at standard deviation of 35 minutes.

Mean difference (min)	Std. dev	n for each quartile	Power (%)
2	35	201	8.8
4	35	201	20.8
6	35	201	40.4
8	35	201	62.9
10	**35**	**201**	**81.7**

CHAPTER 2

THE ASSOCIATION OF GESTATIONAL WEIGHT GAIN WITH CESAREAN DELIVERY RATE AFTER LABOR INDUCTION

Introduction

The rate of labor induction continues to climb and has more than doubled from 9.5% in 1990 to 22.5% in 2006 (71). Labor induction is associated with an increased risk of cesarean delivery(72-75), uterine hyperstimulation, nonreassuring fetal heart rate changes(76) chorioamnionitis and endometritis (77). Furthermore, cesarean delivery after labor induction contributes substantially to maternal and fetal morbidity (78-81).

Higher gestational weight gain may increase the likelihood of cesarean delivery. In previous studies, gestational weight gain has been associated with increased birth weight, macrosomia, large for gestational age (LGA) infants, preeclampsia, and prolonged labor, each of which is associated with cesarean delivery (82). Since overweight and obese women are most likely to gain excess gestational weight(83, 84) and the number of reproductive aged women in these categories continues to increase(85, 86) in the United States, it is appropriate to evaluate gestational weight gain as a risk factor for cesarean delivery after induction of labor.

Several studies have reported an overall increased rate of cesarean delivery associated with higher gestational weight gain without regard for induction (82). However, only two studies reported an increased cesarean delivery rate after labor induction due to higher gestational weight gain (87-91). One of the studies was limited to women with normal pre-pregnancy body mass index (BMI) (87) while the other evaluated weight gain as a unit increase in BMI category over the duration of pregnancy (89).

Substantial weight gain in pregnancy occurs more commonly in overweight and obese women (92). This population of women experiences an increased rate of labor induction and their numbers are growing (85, 85, 86, 88). Given the increasing prevalence of overweight and obese BMI and the serious complications associated with cesarean delivery after induction of labor, it is important to assess the impact of gestational weight gain on failed induction of labor.

Our primary aim was to evaluate the association of gestational weight gain with the cesarean delivery rate in term women undergoing induction of labor. We hypothesize that increased gestational weight gain is associated with a higher risk of cesarean delivery in these women. We were also interested in evaluating how gestational weight gain levels in the population compare with recommendations. The recently published Institute of Medicine (IOM) guidelines indicate that mean weight gain for underweight (<18.5 kg/m^2) women will fall within the recommended range whereas mean weight gain for some women in the normal BMI (18.5 to 24.9 kg/m^2) category and the majority in the overweight (25 to 29.9 kg/m^2) and obese ($\geq$ 30 kg/m^2) categories will exceed the recommended weight gain range. Thus, our secondary aim was to compare the distribution of gestational weight gain in our study sample with respect to the revised IOM recommendations for weight gain during pregnancy (93).

Physiological mechanism

The physiological mechanism by which gestational weight gain may affect the rate of cesarean delivery after labor induction remains unclear however a few possibilities are suggested to explain this association. Gestational weight gain includes contributions from the fetus, placenta, amniotic fluid, uterine and breast hypertrophy, increased blood and extracellular fluid volume and maternal fat storage. In this unique situation, a

physician has to deal with two patients, the mother and the fetus while deciding the optimum amount of gestational weight gain.

The fetus, placenta and amniotic fluid account for approximately 35 percent of the total gestational weight gain(94). Gestational weight gain minus fetal and placental weight is defined as 'absolute weight gain'. An excessive 'absolute weight gain' in non-diabetic, nulliparous women has been shown to increase the risk of cesarean delivery(95)which indicates an independent biological impact of weight gain on failure to deliver vaginally.

Macrosomia associated with excessive gestational weight gain (96) has been linked to an increased risk of cesarean delivery. The independent impact of excessive gestational weight gain on cesarean delivery can be derived from evaluating national trends. A study which evaluated trends in excessive gestational weight gain and cesarean rates between 1990-2000 found that women who gained excessive weight during pregnancy accounted for 24.1% of cesarean in 1990 and 28.1% in 2000 despite the decreasing rates of macrosomia during this period (97).

We believe that women with labor induction should be considered as a separate group because labor induction by itself increases the likelihood of cesarean delivery. Increased gestational weight gain increases the risk of obstructed labor and thereby cesarean delivery by its association with higher infant birth weight (98, 99)and pregnancy induced hypertension(84, 87, 89, 90, 100, 101).

The revised Institute of Medicine (IOM) recommendations for weight gain during pregnancy (93) are based on WHO cutoff points for pre-pregnancy BMI as follows: underweight (< 18.5 kg/m2) 28 to 40 pounds, normal (18.5 - 24.9 kg/m2) 25 to 35 pounds, overweight (25.0 - 29.9 kg/m2) 15 to 25 pounds and obese women (≥ 30.0

kg/m2) 11 to 20 pounds. According to this report, some normal weight women and majority of overweight and obese women will exceed this recommended range. An examination of our study sample for these recommended guidelines is therefore warranted.

Epidemiologic Research

Several studies have evaluated the association between gestational weight gain and cesarean delivery rate and have been reviewed in detail by Vishwanathan *et al.*(82). However, these studies have not examined the association stratified by labor induction. Epidemiological research in the area of gestational weight gain and failure of labor induction or rate of cesarean delivery after induction of labor is sparse. To our knowledge only two studies have examined the relationship between gestational weight gain and cesarean delivery rate after labor induction (87, 89).

The study by DeVader *et al*. (87) was a retrospective analysis of a full term singleton birth cohort in Missouri (n=94,696) using only women with normal pre-pregnancy BMI (19.8 - 26.0 kg/m^2). In a multivariate logistic regression analysis with 25-35 lbs as reference (OR: 1.0), the risk for cesarean was lower with weight gain less than 25 lbs (OR: 0.82; 95% CI: 0.78-0.87) but was higher for weight gain more than 35 lbs (OR: 1.39; 95% CI: 1.29-1.40). However, their restriction of the study sample to women with normal pre-pregnancy BMI and categorization of gestational weight gain limited their findings to a specific BMI category and thus limited their external validity and caused loss of efficiency (102). Devader and colleagues categorized their sample according to the IOM gestational weight gain guidelines of 1990 (<25, 25-35 and >35 lbs) but most women with normal pre-pregnancy BMI usually gain more than the recommended weight (93). Gestational weight gain that was not available through

obstetric data was obtained by maternal recall in this study which may have biased their results.

The second study, by Kabiru *et al*. (89) analyzed a retrospective cohort of 5,131 singleton deliveries with BMI more than 20 kg/m^2 at a single hospital after excluding 398 (7%) women with BMI < 20 and 5,351 (49%) women because of missing pre-pregnancy BMI. The exclusion of almost half of their study population could have biased the results of this study. Using a one way ANOVA test they observed higher rates of cesarean delivery after labor induction in women who had a change in BMI category of one or more than one unit during pregnancy (P<0.001). However, their failure to consider confounding variables, use of categorical exposure and the large percentage of missing data could have biased their results. In contrast, we included consecutive women over three years undergoing labor induction from all categories of pre-pregnancy BMI and also used gestational weight gain as a continuous variable.

Summary

The rate of labor induction in the US has more than doubled from 9.5% in 1990 to 22.5% in 2006 (71). Labor induction is associated with an increased risk of cesarean delivery (72-75) and cesarean delivery after labor induction contributes substantially to both maternal and fetal morbidity (78-81). The limited available evidence revealed a negative effect of excessive gestational weight gain on the cesarean delivery rate after labor induction. Therefore, gestational weight gain should be considered as an important modifiable risk factor for cesarean delivery after failed labor induction.

Excessive absolute weight gain (gestational weight gain minus fetal and placental weight) in nondiabetic, nulliparous women has been shown to increase the risk of cesarean delivery(95)which indicates an independent biological impact of weight gain on

failure to deliver vaginally. Epidemiological evidence on the effect of gestational weight gain on cesarean delivery rate after induction of labor is limited to two studies (87, 89). These studies were limited by use of random categorization, restriction to normal BMI, use of maternal recall (87) and a large amount of missing data or unadjusted analysis (89).

This study will evaluate the influence of gestational weight gain on the cesarean delivery rate in term women undergoing induction of labor using gestational weight gain as a continuous exposure. Our secondary aim is to examine the distribution of gestational weight gain in our study sample with respect to the revised Institute of Medicine recommendations for weight gain during pregnancy (93).

Specific Aims and Hypothesis

Specific Aim To evaluate the effect of gestational weight gain on the rate of cesarean delivery after induction of labor

Hypothesis There is a positive association between gestational weight gain and rate of cesarean delivery after induction of labor.

Secondary Aim To evaluate the distribution of gestational weight gain in our study sample with respect to the revised Institute of Medicine recommendations for weight gain during pregnancy.

Methods

Study Design and Population

We evaluated this association in a retrospective cohort of women who had labor induction between 37 and 42 completed weeks of gestation at Baystate Medical Center, Springfield, Massachusetts. After approval from the Institutional Review Board, obstetric data was collected retrospectively using the Peribirth© obstetrical electronic medical

record system (PeriGen Inc, Princeton, New Jersey). Of the 12,927 deliveries between May 2005 and June 2008, 2,971 (22.9%) women undergoing labor induction were used for this study. After excluding cases with breech presentation (n=20), multiple gestation (n=90), previous cesarean delivery (n=105) and missing information on prepregnancy weight, weight at delivery or height (n=261), we had a final sample size of 2,495. Vacuum extraction and forceps deliveries (n=101) were categorized as vaginal delivery.

Exposure Assessment

Pre-pregnancy weight and height were based on self-reported information during the first prenatal visit. Self reported weight at the time of admission for delivery was used as weight at delivery. In cases where gestational weight gain information was missing in the electronic medical records, the Clinical Information System (CIS) of the hospital was used to retrieve the missing data. If the information was not available in the hospital CIS, individual paper based medical charts (n=998 out of 2,495) were reviewed for the information. For the paper based charts, only the earliest weight from the first trimester was used for pre-pregnancy weight. The last clinic weight measurement or recorded weight from the anesthetic record was used for weight at delivery. Gestational weight gain was calculated as the difference between weight at delivery and pre-pregnancy weight.

Gestational weight gain was evaluated as a categorical as well as continuous variable. However, in the absence of any non-linear association for the final analysis we used gestational weight as continuous variable. Women who lost weight during pregnancy were included with their total weight loss recorded as a negative weight gain. A sensitivity analysis was conducted by excluding these women and analyzing only those with positive weight gain during pregnancy.

Validity of Exposure Assessment

Previous studies have found that self-reported and measured weights are highly correlated among women except they tend to underestimate their weight by approximately 3 lbs (1.36 kg) (103, 104). To detect the error associated with self-reported weight at delivery we conducted a correlation analysis within a subgroup of random women (n = 200) from our study sample. A correlation analysis between the measured weight at the last clinic visit and the self reported weight at delivery was used to evaluate this error.

Outcome Assessment

The information on mode of delivery was obtained from the electronic obstetric database and divided into a binary vaginal and cesarean delivery. Vacuum extraction and forceps deliveries were categorized as vaginal delivery.

Validity of Outcome Assessment

The information on mode of delivery is entered in the electronic obstetric database by a trained medical professional and is cross checked by the billing departments. This information from the electronic obstetric database was retrieved by a trained professional.

Covariate Assessment

Pre-pregnancy BMI was calculated as pre-pregnancy weight in kg divided by height in meters squared. Both pre-pregnancy weight and height was self reported by the patient during the first antenatal care clinic. We categorized BMI as underweight (<18.5 kg/m^2), normal (18.5 - 24.9 kg/m^2), overweight (25 - 29.9 kg/m^2) and obese ($\geq$ 30 kg/m^2) according to the WHO classification. Information regarding maternal age, race, parity, insurance status, gestational age, infant birth weight, infant gender, gestational and

pregestational diabetes mellitus, hypertension, epidural use and type of induction agent were abstracted from the hospital's electronic database. The gestational age estimation at delivery was based on the best clinical estimate calculated by the obstetrician. Various induction agents were broadly categorized as 1) oxytocin only, 2) oxytocin and other agents and 3) other agents only according to their use for individual delivery. The category 'other agents' included misoprostol, dinoprostone, laminaria, artificial rupture of the membranes (AROM) and Foley catheterization.

Bishop score at admission was calculated using the values for cervical dilation, effacement, position, consistency and fetal station (105). This score rates cervical dilation, effacement and fetal station from 0 to 3 and consistency and position from 0 to 2 thus presenting in a range of 0 to 13. We retrieved values of individual components at the time of admission from the database and used them to calculate the score. To categorize Bishop score in a binary variable (favorable or unfavorable) we utilized the area under curve (AUC) of the receiver operating characteristic (ROC) curve. For various possible categories of Bishop score introduced in the multivariable regression model, a maximum AUC of 0.793 was obtained for Bishop score ≤ 5 compared to Bishop score ≥ 6, similar to the traditional cut off points for Bishop score (74). We were able to find and incorporate missing values (n=95) for Bishop scores by reviewing paper based charts from a different prospective study conducted during the same period at the hospital. The indications for induction of labor were divided into six categories namely hypertensive disorders, premature rupture of membranes, post dates, maternal medical complications, fetal compromise and logistic reasons. The indications for cesarean delivery were divided into the following six categories: 1) arrest of dilation/descent, 2)

fetal complications, 3) hypertensive disorders, 4) maternal medical condition, 5) non reassuring fetal heart rate, and 6) patient request/anxiety.

Data Analysis Plan

Univariate analysis

The characteristics of study population are presented as number and percentage (Table 2.1), as are the distribution of indications for induction of labor and cesarean delivery (Table 2.2).

Bivariate analysis

The indications for induction of labor were calculated as percentages and compared between modes of delivery by Fisher's exact test (Table 2.2). The deviation of gestational weight gain from the new IOM recommended guidelines was calculated as percentages above and below the IOM guidelines (Figure 2.1). The unadjusted odds ratios for cesarean delivery after labor induction with gestational weight gain and significant risk factors were calculated using a logistic regression (Table 2.3).

Multivariable analysis

We used multivariable logistic regression analysis to estimate the risk of cesarean delivery for every 5 kg increase in gestational weight gain. To assess confounding, we included each potential confounder in the model. Variables that changed the association between gestational weight gain and risk of cesarean delivery by more than 10% were included in the final multivariable regression model. Parity, age and pre-pregnancy BMI have a significant impact on the physiology of the maternal perineum. Statistical interactions of the effect of gestational weight gain on cesarean risk by parity, maternal age and, pre-pregnancy BMI were assessed using a criterion of $P < 0.10$ for statistical significance (Table 2.3). The Hosmer and Lemeshow goodness of fit test was used to

detect lack of fit for model. Model diagnostics were performed by plotting standardized Pearson residuals and deviance residuals against the predicted probabilities and subject identification number. Variance inflation factor was evaluated to assess multi-collinearity within covariates.

Multiple Imputation for missing Bishop Score information- The Bishop score at admission was calculated using the values for cervical dilation, effacement, position, consistency and fetal station (105). Bishop score for 573 (22.9%) women were not calculated because of missing values for either cervical consistency or position. Methods to address missing data in statistical analysis depend upon the nature of the missing data. Missing data can be classified in three categories 1) Missing Completely at Random (MCAR): missing values are randomly distributed across all observations i.e. reason for missingness is completely unrelated to study variables. 2) Missing at Random (MAR) : missing values are not randomly distributed across all observations but randomly within one or more subsamples i.e. reason for missingness depends only on completely observed variable(s) and 3) Non Ignorable Missingness (NIM): missingness is associated with an incompletely observed variable(s) and cannot be explained by the observed data (106).

In the case of MCAR, a statistical analysis results in unbiased estimates, but if the data is MAR and significantly large (>5%) the estimates are more likely to be biased (106). To deal with MAR values of cervical consistency or position in our data and to utilize all possible information, we used multiple imputation (SAS PROC MI)(107). This procedure incorporates the missing data uncertainty and has been shown to have a relative efficiency of 98% for approximately 20% missing data after 10 iterations (108, 109)(Appendix).

We imputed values for each missing value of cervical consistency and position based on other non missing variables in the data set using SAS procedure PROC MI. These *m*=10 imputed and complete data sets were used for our final multivariable logistic regression model. Parameter estimates from the multivariable logistic regression were obtained by combining the results from 10 imputed data sets using SAS PROC MIANALYZE.

Sample size and Power

Power calculations were performed prior to analysis based on use of a multivariable logistic regression of mode of delivery (cesarean rate=23.5%) on a continuous, normally distributed gestational weight gain. In these calculations, we determined that our analysis using the available sample size of 2495 can detect an odds ratio of 1.15 with approximately 80% power at a 0.05 significance level (Table 2.6).

Missing Data Analysis

The women who had a singleton term delivery but were missing information on pre-pregnancy weight, weight at delivery or height were compared with women in our study who were not missing that data to determine if there were any significant differences among important predictors of failed labor induction such as gestational age, parity, bishop score and infant gender. A chi square or Fisher's exact analysis was used to determine the difference in maternal and obstetric characteristics respectively (Table 2.5).

Results

The mean ± standard deviation of gestational weight gain for the study sample was 14.4 (±7) kg with a range of -13.6 to 63.0 kg. Nearly a quarter (23.5%) of the induced women were delivered by cesarean and had significantly higher gestational

weight gain than those who had vaginal delivery (15.4 ± 7.5 kg *vs*. 14.1 ± 6.9 kg; *P* <0.0001). The mean age of women in the study was 27.3 (± 6.4) years and it was not significantly different across mode of delivery (27.4 ± 6.4 *vs*. 27.3 ± 6.6; *P*=0.82). The mean pre-pregnancy BMI was 27.2 ± 6.7 kg/m^2 for the study sample and women from the cesarean group had significantly higher pre-pregnancy BMI than those who delivered vaginally (29.4 ± 7.8 kg/m^2 *vs*. 26.6 ± 6.1 kg/m^2; *P*<0.0001).

The majority of women in the study reported themselves as white (75.7%). Infants born by cesarean were heavier than those born vaginally (3530.2 ± 538.3 g *vs.* 3407 ± 477 g; *P* <0.0001). Longer gestation, nulliparity, unfavorable Bishop score (≤ 5) at admission, and male infant gender were also associated with cesarean delivery in induced women (Table 2.1). A total of 360 women were missing information regarding indication for induction of labor (IOL) and postdates was the most common indication for IOL (Table 2.2).

In multivariable analysis, the odds of cesarean delivery were 13% higher for every 5 kg (11 lb) increase in gestational weight gain (OR 1.13, 95% CI 1.05-1.23) (Table 2.3). The odds of cesarean delivery after labor induction were significantly higher with every unit increase in maternal age (OR 1.05, 95% CI 1.03-1.06) and pre-pregnancy BMI (OR 1.08, 95% CI 1.06-1.10). Nulliparity (OR 9.13, 95% CI 7.00-11.90), an unfavorable Bishop score (≤ 5) at admission (OR 2.30, 95% CI 1.90-2.90) and a male infant (OR 1.37, 95% CI 1.10-1.70) also were associated with significantly increased likelihood of cesarean delivery. However, cesarean delivery was not associated with gestational age (Table 2.3).

We assessed interactions by parity, maternal age, infant birth weight, pre-pregnancy BMI and Bishop score for the association between gestational weight gain and

risk of cesarean delivery. These findings were not statistically significant ($P_{interaction} > 0.10$). The positive association between gestational weight gain and cesarean delivery was consistent across strata of BMI, parity, age and birth weight. Our primary analysis included women who had lost weight during pregnancy (n=29). Our results were materially unchanged in analyses limited to women who did not lose weight during pregnancy (n=2,466).

We compared the distribution of multiple variables between subjects with all available Bishop score components to subjects with either cervical consistency or position data missing (n=573). Participants with missing information were similar to those with complete Bishop score information in terms of gestational weight gain, mode of delivery, maternal age, gestational age, infant birth weight, pre-pregnancy BMI and parity. A separate analysis without multiple imputation yielded a similar association between gestational weight gain and risk of cesarean delivery.

Distribution of gestational weight gain according to the revised Institute of Medicine (IOM) guidelines shows that the mean weight gain (17.5 ± 7.2 kg) for women in the underweight category fell within the recommended weight range, whereas the mean weight gain for women in the normal (16.1 ± 6.2 kg), overweight (14.4 ± 6.7 kg) and obese (11.6 ± 7.6 kg) BMI categories exceeded the recommended range (Fig 2.1). There was a significantly higher risk of cesarean for those whose weight gain during pregnancy was above the recommended IOM guidelines (Table 2.4).

Women excluded due to missing information on pre-pregnancy weight, weight at delivery or height (n=261) were compared to women with known information. There were no significant differences observed in maternal and fetal characteristics except for maternal age and use of epidural analgesia. Those missing information on pre-pregnancy

weight, height or weight at delivery were older and less likely to receive epidural analgesia during delivery (Table 2.5). To detect the error associated with self-reported weight at delivery we conducted a correlation analysis within a subgroup of random women (n=172) from this sample. There was a high correlation (r=0.994) between the measured weight at the last clinic visit and the self reported weight at delivery where the mean difference between two measurements was 6 ± 6.19 days.

Discussion

In this retrospective study, we found that for every 5 kg increase in gestational weight gain, the risk for cesarean delivery increased by 13% in women with a singleton pregnancy that underwent induction of labor. This increase was not significantly different across strata defined by parity, maternal age, birth weight, Bishop score, or pre-pregnancy BMI ($P_{interaction} > 0.10$). Our results were similar to the two studies that also revealed an increased risk for cesarean delivery after induction of labor with increased gestational weight gain (87, 89). The study by DeVader *et al.* (87), a retrospective analysis of full term singleton birth cohort in Missouri (n=94,696) found that the rate of cesarean delivery with labor induction was higher in women who gained > 35 lbs (15.87 kg) and lower for women who gained < 25 lbs (11.34 kg) compared to women who gained 25 to 35 lbs (11.34-15.87 kg) during pregnancy.

Categorization of self-reported gestational weight gain is a problem because it results in loss of efficiency as well as potential misclassification due to recall errors, digit preference, and rounding errors. We minimized this risk by using gestational weight gain as a continuous exposure. The second study by Kabiru *et al.* (89) analyzed a retrospective cohort of 5,131 singleton deliveries with maternal BMI ≥ 20 kg/m^2 at a single hospital after excluding 5,351 (49%) women because of missing pre-pregnancy BMI. Using a

one way ANOVA test they observed higher rates of cesarean delivery after induction in women who had a change in BMI category of ≥ 1 unit during pregnancy. However, their findings were limited by an unadjusted analysis, categorical exposure and exclusion of nearly half of the sample due to missing data. These limitations could have biased their results in either side of the null. In our study, we included consecutive deliveries over three years in a cohort of women undergoing labor induction and from all categories of pre-pregnancy BMI. We also used gestational weight gain as a continuous variable and adjusted for possible significant confounders.

Values for cervical consistency or position were missing for 22.9% of women in our study. In order to address this missingness, we used multiple imputation, generating 10 imputed datasets and performing analyses on those imputed datasets. This procedure has been shown to have an efficiency of 98% for 22.9% missing data after 10 iterations (108). Almost 10% of the women (n=261) in our cohort were excluded for lack of information on prepregnancy weight, height or weight at delivery. Our analysis showed that these women were similar to the rest of the cohort included for analysis with respect to maternal and fetal characteristics except for age and use of epidural analgesia. Women excluded from the study were more likely to be older and less likely to have epidural analgesia. Since there was no significant difference between the two samples regarding their modes of delivery, if the excluded sample had gained excessive weight, their exclusion could have led to an overestimation of the effect. If the excluded sample had gained less weight, their exclusion could have led to an underestimation of the effect. However, we believe that this bias would be minimal because we expect the difference in gestational weight gain between these two groups to be non-significant.

Similar to other studies, we noted higher rates of cesarean delivery after induction associated with higher age,(74, 110), higher pre-pregnancy BMI,(73, 74), nulliparity,(111-113) and unfavorable Bishop score (111) .The significantly higher cesarean delivery risk after induction for male infants detected in our study appears to be a novel finding. This may be secondary to an overall increased risk for cesarean delivery among male infants(114) or uncontrolled confounding by fetal indications for cesarean delivery such as dystocia,(115, 116), cord problems(117) and fetal distress(118) that are associated with male infants. The recently published IOM guidelines(93) indicate that mean weight gain of underweight women will fall within the recommended range whereas some women in the normal BMI category and the majority in the overweight and obese categories will exceed the recommended weight gain range, which concur with our results.

Some limitations of our study should be noted. Pre-pregnancy weight was either self reported (n=1,497) or obtained at the first prenatal visit in the first trimester (n=998). Similar to our high correlation (r=0.99) findings from analysis of a random sample of 172 women in our data, previous studies have also found that self-reported and measured weights are highly correlated except that women tend to underestimate their weight by approximately 3 lbs (1.36 kg) (103, 104). Any underestimation of gestational weight gain in our study would be unrelated to the mode of delivery thus lead to non-differential and independent misclassification. Because of our use of continuous exposure variable, there is a possibility of a bias away from the null (119-122).The possibility of a bias away from the null due to misclassification of BMI has been quantified in prior studies using a probabilistic bias analysis(123); we expect such misclassification to have been minimal in our study and to therefore have had little effect.

Human weight varies throughout the day and even more variations are observed in pregnant women due to the heightened levels of corticotrophin hormones, ACTH and cortisol (124). Assuming that the pre-pregnancy weight reported was measured at the minimum threshold of that day's weight and the weight at delivery was measured at the maximum threshold of that day's weight the gestational weight gain would be the maximum possible for that woman and *vice versa*. This measurement error is unavoidable, minimal and is not associated with the outcome. Therefore, it would only minimally alter the effect estimate by biasing it towards the null.

All pregnant women have a weekly weight measurement from 36 week onwards at Baystate Medical Center. If weight measurements in high risk cases are done more accurately than low risk cases and we assume uniform underreporting of weight by women, this systematic difference in weight measurement could *increase the observed gestational weight gain* for those who are *more likely to have a cesarean delivery* thus inflating the higher category of exposure among those who had a cesarean delivery. Although this differential misclassification of gestational weight gain across mode of delivery is expected to be minimal, it could have biased the effect estimate on either side of the null.

We did not find a significant interaction effect by pre-pregnancy BMI and indication for induction. It should be noted that our power to detect interaction was limited due to small sample sizes caused by stratification. After collapsing pre-pregnancy BMI into <25 kg/m^2 and ≥ 25 kg/m^2, no significant interaction effect was observed. It should also be remembered that gestational weight gain is a continuous process throughout pregnancy and it is difficult to differentiate between maternal and fetal components of the weight gain. It is also important to evaluate the weight gain at regular

interval during pregnancy to estimate the most important period of weight gain. Our study was limited by its retrospective design and based on the assumption that gestational weight gain in its entirety impacts the rate of cesarean delivery.

In summary, after adjusting for risk factors associated with cesarean delivery after induction of labor, increased gestational weight gain was associated with an increased rate of cesarean delivery among induced women. Prospectively designed studies with weight measurements at regular intervals during pregnancy and, appropriate adjustment for confounding variables are needed to provide health care providers with data necessary to make informed recommendations.

Significance

The positive association of gestational weight gain with an increased rate of cesarean delivery found in our study could be a primary effect of weight gain or a mediation effect through various indications for cesarean delivery such as increased birth weight, macrosomia, large for gestational age (LGA) infants, preeclampsia or prolonged labor that are associated with higher gestational weight gain (82). However, the modifiable nature of gestational weight gain makes it an important prognostic factor for cesarean delivery. Our study was conducted in a predominantly Caucasian population from a single health center in Massachusetts. In analyses of effect modification we did not observe findings to differ in our sample by race. The mechanism by which gestational weight gain increases risk of cesarean delivery is likely consistent by race and ethnicity; however future studies may consider this question in select populations. Our findings underscore the importance of examining gestational weight gain across all categories of BMI since a substantial proportion of women are overweight or obese entering pregnancy and are likely to exceed the IOM weight gain guidelines.

Human Subjects

The Gestational Weight Gain Study was approved by the Institutional Review Boards of Baystate Medical Center. The electronic medical records were retrieved without any identifier so that there was no threat to patient's privacy. The paper based medical charts were used to retrieve missing information on height and gestational weight gain. Only trained personnel were allowed to access the medical charts only in the hospital records room to ensure the safety of patient information.

Every effort was made to ensure that confidential information remained secure. Study personnel were trained in privacy protocols and abstracted data sets and medical records forms were kept under lock and key. Computer files were kept on a secure server which was password protected, with only study personnel able to access the files.

There were no known risks to participants, with the exception of breach of confidentiality. Given that all study personnel were trained in privacy procedures, this was unlikely to occur. There were no known benefits to participation with the exception of advancement in science.

Permission to Access Data

Baystate Medical Center approved the research proposal in May 2008 and there was an annual renewal of this project until May 2011

Table 2.1 Distribution of maternal and fetal characteristics according to mode of delivery among women who had induction of labor (n=2,495)

Characteristic	Total(n=2,495) n (%)	Vaginal (n=1,909) n (%)	Cesarean (n=586) n (%)	*P Value#*
Age (years)				
≤20	455 (18.2)	340 (17.8)	115 (19.6)	0.11
21-25	529 (21.2)	396 (20.7)	133 (22.7)	
26-30	691 (27.7)	549 (28.8)	142 (24.2)	
31-35	545 (21.8)	414 (21.7)	131 (22.4)	
36-40	236 (9.5)	185 (9.7)	51 (8.7)	
>40	39 (1.6)	25 (1.3)	14 (2.4)	
Race[a]				
Black	251 (10.8)	182 (10.3)	69 (12.4)	0.13
Hispanic	259 (11.2)	199 (11.3)	60 (10.8)	
White	1,757 (75.7)	1,348 (76.3)	409 (73.7)	
Others[b]	55 (2.3)	38 (2.1)	17 (3.1)	
Gestational age (weeks)				
37 – 39	1,385 (55.5)	1,128 (59.1)	257 (43.9)	<0.0001
40 – 42	1,110 (44.5)	781 (40.9)	329 (56.1)	
Birth weight (g)				
<2,500	94 (3.8)	66 (3.5)	28 (4.8)	<0.0001
2,500-4,000	2,101 (84.2)	1,645 (86.1)	456 (77.8)	
>4,000	300 (12)	198 (10.4)	102 (17.4)	
Parity				
Nulliparous	1,290 (51.7)	802 (42.0)	488 (83.3)	<0.0001
Multiparous	1,205 (48.3)	1,107 (58.0)	98 (16.7)	
Bishop score				
0-5	1,061 (55.2)	758 (51.1)	303 (69.2)	<0.0001
6-12	861 (44.8)	726 (48.9)	135 (30.8)	
Infant Gender				
Female	1,252 (50.2)	999 (52.3)	253 (43.2)	<0.0001
Male	1,243 (48.8)	910 (47.7)	333 (56.8)	
Prepregnancy BMI (kg/m^2)				
< 18.5	77 (3.1)	67 (3.5)	10 (1.7)	<0.0001
18.5-24.9	1,035 (41.5)	839 (43.9)	196 (33.5)	
25-29.9	684 (27.4)	537 (28.1)	147 (25.1)	
≥ 30	699 (28.0)	466 (24.5)	233 (39.7)	
Gestational Diabetes				
Yes	223 (8.9)	165 (8.6)	58 (9.9)	0.35
No	2,272 (91.1)	1,744 (91.4)	528 (90.1)	
Pregestational Diabetes				
Yes	30 (1.2)	19 (1)	11 (1.9)	0.08
No	2465 (98.8)	1890 (99)	575 (98.1)	
Hypertension				
Yes	190 (7.6)	132 (6.9)	58 (9.9)	0.01
No	2305 (92.4)	1777 (93.1)	528 (90.1)	
Induction agents				
Only Oxytocin	1,318 (52.8)	1,092 (57.2)	226 (38.6)	<0.0001
Oxytocin + Other agents[c]	957 (38.4)	665 (34.8)	292 (49.8)	
Only Other agents[c]	220 (8.8)	152 (8)	68 (11.6)	

Epidural analgesia				
Yes	2109 (84.5)	1641 (86)	468 (79.9)	<0.0001
No	386 (15.5)	268 (14)	118 (20.1)	
Insurance Status				
Public	1038 (41.6)	811 (42.5)	227 (38.7)	0.11
Private	1457 (58.4)	1098 (57.5)	359 (61.3)	

P value from chi squared, except Fisher's exact test for prepregnancy BMI

[a] Numbers do not total to 2,495 because of missing data.

[b] Women who reported themselves as Asian, Native American, Multiracial or Other.

[c] Misoprostol, dinoprostone, Foley catheter, laminaria, artificial rupture of membranes.

Table 2.2 Indications for induction and cesarean delivery among women who had induction of labor (n=2,495)

Indications	Total (n=2,495) No. (%)	Vaginal (n=1,909) No. (%)	Cesarean (n=586) No. (%)	P Value#
Indication for Induction[a]				
Hypertensive disorders	177 (8.3)	124 (7.8)	53 (9.9)	0.0025
Premature rupture of membranes	110 (5.2)	84 (5.3)	26 (4.8)	
Post dates	944 (44.2)	681 (42.6)	263 (48.9)	
Maternal medical conditions	275 (12.9)	200 (12.5)	75 (13.9)	
Fetal compromise	279 (13.1)	224 (14.0)	55 (10.2)	
Logistic reasons	350 (16.3)	284 (17.8)	66 (12.3)	
Indication for Cesarean Delivery				
Arrest of Dilation/Descent	398 (67.9)	–	398 (67.9)	–
Fetal Complications	39 (6.7)	–	39 (6.7)	
Hypertensive disorders	14 (2.4)	–	14 (2.4)	
Maternal medical conditions	20 (3.4)	–	20 (3.4)	
Non reassuring fetal heart rate	110 (18.8)	–	110 (18.8)	
Patients request/ anxiety	5 (0.9)	–	5 (0.9)	

P value from Fisher's exact test

[a] Numbers do not total to 2,495 because of missing data.

Table 2.3 Unadjusted and adjusted odds ratios for gestational weight gain and other maternal and fetal factors associated with cesarean delivery among term labor inductions (n=2,495)

Risk factors	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Gestational weight gain		
Every 5kg (11 lb) increase	1.14 (1.07-1.22)	1.13 (1.05-1.23)
Other risk factors		
Maternal age in years (unit increase)	1.00 (0.98-1.01)	1.05 (1.03-1.06)
Birth weight (100 g increase)	1.05 (1.03-1.07)	1.05 (1.03-1.08)
Gestational age (week increase)	1.16 (1.08-1.24)	1.01 (0.95-1.07)
Prepregnancy BMI (kg/m^2) (unit increase)	1.06 (1.05-1.07)	1.08 (1.06-1.10)
Parity		
Nulliparous	6.87 (5.43-8.69)	9.13 (7.00-11.90)
Parous	1.00[b]	1.00[b]
Bishop score		
≤ 5 (unfavorable)	2.30 (1.80-2.80)	2.30 (1.90-2.90)
≥ 6 (favorable)	1.00[b]	1.00[b]
Infant Gender		
Male	1.44 (1.20-1.74)	1.37 (1.10-1.70)
Female	1.00[b]	1.00[b]

Abbreviations: OR, odds ratio; CI, confidence interval;

[a] Adjusted for gestational weight gain, maternal age, birth weight, gestational age, prepregnancy BMI, parity, bishop score and infant gender.

[b] Reference group for the exposure variable

Figure 2.1 The 2009 Institute of Medicine (IOM) guidelines for total weight gain during pregnancy and respective distribution of gestational weight gain among women who had induction of labor (n=2,495)

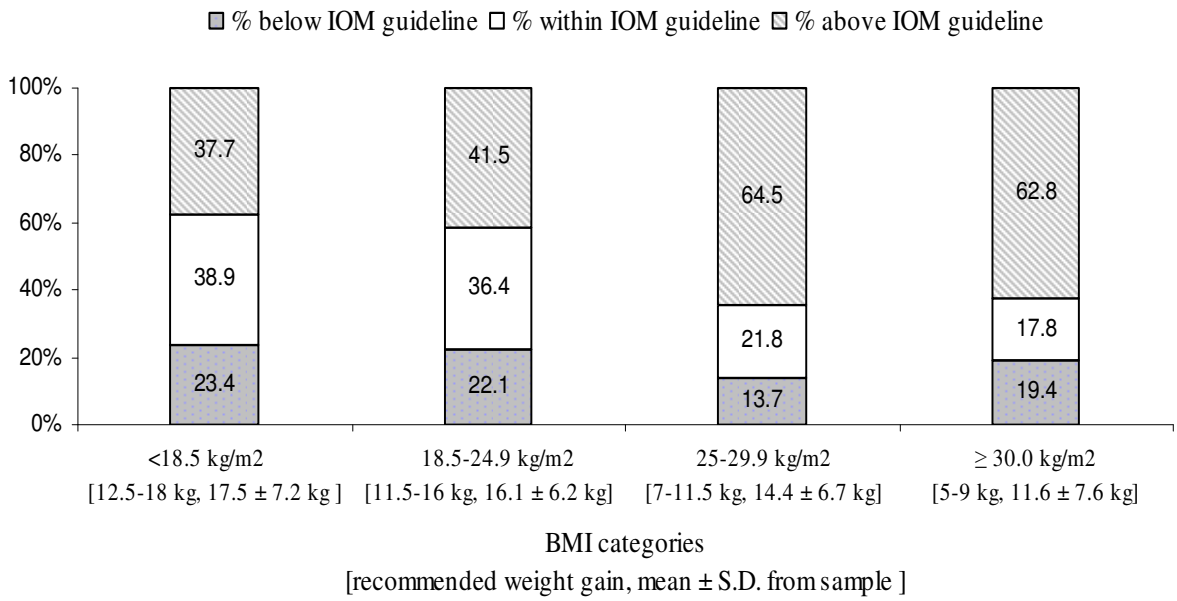


Table 2.4 Distribution of mode of delivery in women with gestational weight gain below, within or above the revised 2009 IOM guidelines

BMI categories according to IOM classification	N=2,495 n (%)	wt. gain below the IOM guideline		wt. gain within the IOM guideline		wt. gain above the IOM guideline	
		Total n (%)		Total n (%)		Total n (%)	
		Cesarean n (%)	Vaginal n (%)	**Cesarean n (%)**	Vaginal n (%)	**Cesarean n (%)**	Vaginal n (%)
<18.5 kg/m2	77 (3.1)	18 (23.4)		30 (38.9)		29 (37.7)	
		0 (0)	18 (100)	**4 (13.3)**	26 (86.7)	**6 (20.7)**	23 (79.3)
18.5-24.9 kg/m2	1,035 (41.5)	229 (22.1)		376 (36.4)		430 (41.5)	
		33 (14.4)	196 (85.6)	**58 (15.4)**	318 (84.6)	**105 (24.4)**	325 (75.6)
25-29.9 kg/m2	684 (27.4)	94 (13.7)		149 (21.8)		441 (64.5)	
		12 (12.8)	82 (87.2)	**34 (22.8)**	115 (77.2)	**101 (22.9)**	340 (77.1)
≥ 30.0 kg/m2	699 (28)	136 (19.4)		124 (17.8)		439 (62.8)	
		27 (19.9)	109 (80.1)	**39 (31.4)**	85 (68.6)	**167 (38.0)**	272 (62.0)

Table 2.5 Comparison of maternal and obstetric characteristics between study sample and the sample excluded because of missing pre-pregnancy weight, height or weight at delivery.

Characteristic	Total (n=2,495)	Missing (n=261)	*P Value#*
Mode of Delivery			
Vaginal	1909 (76.5)	195 (74.7)	0.51
Cesarean	586 (23.5)	66 (25.3)	
Age (years)			
≤20	455 (18.2)	28(10.7)	0.03
21-25	529 (21.2)	43(16.5)	
26-30	691 (27.7)	79(30.3)	
31-35	545 (21.8)	74(28.3)	
36-40	236 (9.5)	30(11.5)	
>40	39 (1.6)	7(2.7)	
Race			
Black	251 (10.8)	18 (7.2)	0.21
Hispanic	259 (11.2)	23 (9.2)	
White	1,757 (75.7)	202 (80.4)	
Others*	55 (2.3)	8 (3.2)	
Gestational age (weeks)			
37 – 39	1,385 (55.5)	141 (54.0)	0.64
40 – 42	1,110 (44.5)	120 (46.0)	
Birth weight (g)			
<2,500	94 (3.8)	6 (2.3)	0.47
2,500-4,000	2,101 (84.2)	221 (85.0)	
>4,000	300 (12)	33 (12.7)	
Parity			
Nulliparous	1,290 (51.7)	130 (50.0)	0.60
Multiparous	1,205 (48.3)	130 (50.0)	
Bishop score			
0-5	1,061 (55.2)	92 (49.7)	0.15
6-12	861 (44.8)	93 (50.3)	
Infant Gender			
Female	1,252 (50.2)	122 (46.9)	0.31
Male	1,243 (48.8)	138 (53.1)	
Gestational Diabetes			
Yes	223 (8.9)	21 (8.1)	0.62
No	2,272 (91.1)	240 (92.9)	
Pregestational Diabetes			
Yes	30 (1.2)	3 (1.1)	0.93
No	2465 (98.8)	258 (98.9)	
Hypertension			
Yes	190 (7.6)	19 (6.9)	0.84
No	2305 (92.4)	242 (93.1)	
Epidural analgesia			
Yes	2109 (84.5)	198 (75.8)	0.0003
No	386 (15.5)	63 (24.2)	
Insurance Status			
Public	1038 (41.6)	120 (45.9)	0.17
Private	1457 (58.4)	141 (54.1)	

Data presented as n (%), # *P* value from chi squared test, * Asian, Native American, Multiracial or Other

Table 2.6 Calculation of sample size for a logistic regression analysis at 80% power and 0.05 significance level.

P0*	Odds Ratio	N	Power
0.235	1.05	2495	0.156
0.235	1.10	2495	0.460
0.235	1.15	2495	0.778
0.235	1.20	2495	0.945
0.235	1.25	2495	0.991

*P0=probability of cesarean delivery at mean gestational weight gain

CHAPTER 3

THE EFFECT OF MODE OF DELIVERY AND DURATION OF SECOND STAGE OF LABOR ON INTRAVENTRICULAR HEMORRHAGE IN INFANTS WEIGHING LESS THAN 1500 GRAMS OR BORN BEFORE 30 WEEKS OF GESTATION

Introduction

The number of infants delivered before 28 weeks of gestation has increased from 0.71% in 1990 to 0.76% in 2006(71). Survival in this population has improved because of advances in assisted ventilation, use of antenatal steroids and surfactant therapy (125). However, significant concerns remain regarding intraventricular hemorrhage (IVH), one of the most common conditions among early preterm births (126, 127). IVH is a bleeding into the ventricular system of the brain and is a common morbidity among infants in this population with incidence estimates ranging from 23% (128) to 27% (129) among very low birth weight (VLBW; < 1500 grams) infants in the United States. It is also an important predictor of cerebral palsy and neurodevelopmental delay (130). Intraventricular hemorrhage in VLBW infants originates from the subependymal germinal matrix which is a source of neuronal and glial precursors. The germinal matrix is highly vascular but pericyte (131) and basement membrane protein (132) deficient structure. IVH is often classified by severity using Papile classification in four grades 1 to 4 (133) with Grades 3 and 4 often grouped together as severe IVH.

Although a significant number of preterm births are iatrogenic (28%), resulting from treatment of conditions including preeclampsia, fetal distress, fetal growth restriction, abruptio placentae and fetal demise, the majority of preterm births (72%)

result from spontaneous preterm labor with or without preterm premature rupture of membrane (PPROM) (134). The second stage of labor, defined as the period between complete dilation of the cervix and delivery of the fetus is a potentially risky period for premature fetus. During this stage the fetus passes through the narrow interspinous diameter (135) and is exposed to sudden pressure changes (136) and increased intracranial pressure (12).The active phase of labor, defined as the period between 5 to 8 cm dilation (137) has been associated with increased risk of IVH among the newborns weighing less than 1750 g (138, 139) but no prior studies have evaluated the association between duration of the second stage of labor and IVH in very low birth weight infants.

The effect of mode of delivery on risk of developing IVH in early preterm births is conflicting. Several prospective (140, 141)and retrospective(142-145) studies have concluded that vaginal delivery increases the risk of IVH in early preterm infants. However, several other observational studies have found no association between mode of delivery and IVH (146-150). A few studies have shown a significant reduction in risk of IVH associated with cesarean delivery in preterm infants (151), and very low birth weight infants (152). The increased risk with vaginal delivery suggests a possible association with external physical trauma during delivery which may be associated with duration of second stage of labor. However, few studies have examined the effect of vaginal delivery on clinically severe grade 3 and 4 of IVH since the introduction of surfactant when the survival rates among infants with IVH significantly increased (153).

Given the conflicting evidence of the effect of mode of delivery and absent evidence of the effect of duration of labor on IVH in very preterm births, it is imperative to evaluate this association in the steadily increasing population of very preterm births. Therefore, we evaluated the effect of mode of delivery and duration of second stage of

labor on IVH among singleton infants born before 30 weeks of gestation or with birth weight less than 1500 g using the Vermont Oxford Network Database from Baystate Medical Center at Springfield, MA. We hypothesize that vaginal delivery and duration of second stage of labor would be associated with an increased risk of IVH.

Physiological mechanism

An IVH in very low birth weights (VLBW) infants originates predominantly from the highly vascular but pericyte (131) and basement membrane protein (132) deficient structure called the subependymal germinal matrix which is a source of neuronal and glial precursors. Intraventricular hemorrhage is classified according to its severity into four grades as follows; Grade 1 is sub-ependymal hemorrhage (SEH) with no blood clot in the ventricular lumen., grade 2 is blood within the lumen without ventricular dilation, grade 3 represents IVH with ventricular enlargement and grade 4 is IVH along with parenchymal hemorrhagic infarction (133). Because grade 3 and grade 4 IVH are associated with severe long term morbidity, they are often grouped together as severe IVH.

The physiological mechanism by which mode of delivery and second stage of labor may affect IVH is unclear. Some of the proposed pathways for IVH development include cytokine disruption of fetal perfusion, damage by oxygen free radicals, loss of cerebral autoregulation and, abrupt alterations in blood pressure leading to capillary bleeding (154). However, the most likely explanation for the effect of vaginal delivery, especially second stage of labor, on the risk of IVH is the physical pressure and release of cortisol and catcholamines that occurs during passage of fetus through the maternal pelvis during labor.

In terms of the physical pressure mechanism, Schwartz *et. al.* (1927) proposed

that the pressure difference in the presenting part and the rest of the body during vaginal delivery was responsible for intracranial hemorrhage (155). Physiologically, the increased intracranial pressure (12) and sudden pressure changes experienced by the fetal head during vaginal delivery (136, 156) may lead to a fall in cerebral blood flow. This may be followed by a blood flow redistribution (157) causing hemorrhage in the pressure passive and basement membrane protein deficient germinal matrix that is unable to autoregulate the cerebral blood flow (133, 158). Another hypothesis is that uterine contractions during vaginal delivery compress the maternal spiral arteries leading to hypoxia (159). The fetal acidosis resulting due to prolonged second stage at birth may initiate IVH or exacerbate existing IVH.

In terms of the cortisol and catecholamines pathway, vaginal delivery has been shown to be associated with elevated fetal stress compared to elective cesarean delivery (160). Elevated fetal stress leads to the higher levels of fetal catecholamines and cortisols in vaginal deliveries compared to cesarean (161), especially among preterm births (160, 162). These high cortisol (163, 164) and catecholamines (165) values have been associated with a higher risk of severe grade IVH in very preterm births.

Epidemiological Research

Mode of delivery and IVH

IVH all grades

Epidemiological research regarding mode of delivery and IVH is conflicting. Although several studies (140-145, 150) have reported that vaginal delivery increases the risk of IVH in early preterm births, many observational studies have found no association between mode of delivery and IVH (146-149). Anderson *et al*., (1988) found that irrespective of mode of delivery the exposure to active phase of labor (interval

between 5 cm cervical dilation and time of delivery) was associated with higher risk for IVH. In their study sample (n=89) of infants with birth weight < 1500 g, the proportion of early IVH was 26 out of 63 (41.3%) for exposure to active phase 2 out of 26 (7.7%) for exposure to no active phase. The progression of an early IVH from grades 1 and 2 to grades 3 or 4 was higher among those exposed to active phase (54%) than those not exposed to active phase (0%). In a different study, the same research group also found that the risk of late IVH increased in the following order; vaginal with forceps (OR: 1.0 as Reference), vaginal with no forceps (OR: 3.4 (95% CI: 0.6, 19.4)), cesarean with no labor (OR: 6.6 (95% CI: 1.1, 38.9)), cesarean with latent phase (OR: 7.4 (95% CI: 1.1,48.3)) and cesarean with active phase (OR: 9.1 (95% CI: 1.4, 58.2) (138). This suggests that the exposure to labor, especially active phase is more important than the mode of delivery.

Severe IVH (grades 3 and 4):

Although several studies have examined the effect of vaginal delivery on IVH, very few have examined its effect on the rate of clinically significant grades 3 and 4 of IVH in the post-surfactant era after 1990 (166)when the survival with IVH significantly increased(153). We conducted a systematic review of studies with analysis adjusting for at least gestational age and infant birth weight as bias due to confounding plays an essential role in the estimation of the true estimate (167) especially, in early preterm deliveries (168). After screening 227 articles, a total of four studies(148, 169-171) met our inclusion criteria.

There were 3 retrospective cohorts (148, 169, 170), and 1 matched case control study(171) (Table 3.1). The crude summary odds ratio from four studies (148, 169-171) with available unadjusted results using a random effect model revealed a significant

increase in the risk of IVH for vaginal delivery compared to cesarean (odds ratio [OR]=1.75 (95% Confidence Interval [CI]:1.47, 2.09) with a non significant heterogeneity variance of 0.002 at p=0.37. The summary odds ratio from analysis adjusted for confounding factors yielded a non-statistically significant association between vaginal delivery and severe IVH (OR= 1.08 (95% CI: 0.88, 1.33) as compared to cesarean delivery. The estimated heterogeneity variance was non-significant at 0.00 with a p value of 0.48, suggesting no statistically significant differences among the evaluated studies. A forest plot displaying these results is presented in Figure 3.1.

The most recent study conducted in Italy examined the association between mode of delivery and IVH using a sample of 218 infants including 52 twins born before 28 weeks of gestation (145).The authors found a significant protective effect of cesarean as compared to vaginal delivery (RR: 0.42, 95% CI: 0.28-0.63) for all grades of IVH in a multivariable analysis. After stratification by IVH the protective effect of cesarean was significant only for grade 3 IVH (18% *vs.* 2%). Inclusion of twins in this study without a separate analysis for twins could have biased the results.

A meta-analysis of six randomized controlled trials (RCT) found no protective effect of cesarean delivery against intracranial pathology in comparison with vaginal delivery (172). Also, these six trials included only 122 women and faced problems such as drop outs and cross over from the intervention arm.

Duration of second stage and IVH

The labor is divided in three different stages beginning from onset of contractions to time of delivery. The first stage constitutes the period between onset of uterine contractions and complete dilation of uterine cervix to 10 cm. The second stage of labor begins at 10 cm dilation and ends with complete fetal delivery. The third stage ends with

complete expulsion of placenta (135). To our knowledge, no study has examined the association between duration of second stage and IVH. The two studies which evaluated the effect of active phase of labor (a part of first stage of labor with an interval between 5-10 cm dilation) on IVH found an increased risk of grade 3 and 4 IVH after exposure to the active phase compared to those not exposed to active phase of labor (139, 173). Two prospective studies evaluated the association between exposure to labor in its entirety and risk of IVH (138, 150).

In the most recent study, the Developmental Epidemiology Network investigators evaluated the association between duration of labor (i.e. period between onset of contractions to time of delivery) and IVH using a prospectively collected sample of 1588 infants weighing less than 1500 g at birth(150). In an unadjusted analysis, the risk of IVH for vaginal delivery with ≤ 12 hour labor and > 12 hour labor was 24% and 30% respectively. Whereas, the risk of IVH for cesarean delivery after exposure to no labor, ≤ 12 hour labor and > 12 hour labor was 9%, 15% and 17% respectively. Thus, exposure to labor increased the risk of IVH and this risk increased with increased duration of labor. After controlling for gestational age, birth weight for gestational age, antenatal corticosteroids and fetal vasculitis the authors observed an increasing but non-significant trend for risk of IVH after no labor (RR: 1, reference), ≤ 12 hours (RR: 1.1, 95% CI: 0.7-1.8) and > 12 hours (RR: 1.6, 95% CI: 1.0-2.6). Although this was the largest study, the authors evaluated the entire duration of labor with no specific emphasis on the second stage. Evaluation of the first stage of labor may result in exposure misclassification because it is difficult to accurately quantify and many of women undergo contractions for hours before entering labor. Also, by not stratifying the

association by first and second stage of labor, authors may have overlooked the differential stress levels associated with these stages.

The study by Shaver *et al.* (1992) (138) prospectively evaluated the risk of IVH using prospectively enrolled 230 infants including 19 pairs of twins who had an estimated fetal weight of less than 1750 g. As compared to vaginal delivery with forceps the authors found an increased risk of IVH for vaginal delivery with no forceps (OR: 3.4, 95% CI: 0.6 - 19.4), cesarean with no labor (OR: 6.6, 95% CI: 1.1 – 38.9), cesarean latent phase (OR: 7.4, 95% CI: 1.1 - 48.3) cesarean active phase (OR: 9.1, 95% CI:1.4-58.2). Although this study was the first to purport the risk of active phase of labor on IVH it lacked sufficient power to perform a multivariable analysis and, failed to adjust for gestational age and stratify results by multiple gestations.

Summary

In summary, the higher incidence of grade 3 and 4 of IVH in preterm infants (174) and the association between IVH and neurodevelopmental morbidity (130, 175-177) and mortality (127, 178) stresses the importance of considering the possible contribution of modifiable factors such as mode of delivery on risk of IVH. Second stage of labor has been associated with fetal morbidity and is the most crucial part of labor. However, there is no current knowledge regarding the effect of duration of second stage of labor as a risk factor for IVH. Therefore, we evaluated the effect of mode of delivery and duration of second stage of labor on the risk of IVH among infants born before 30 weeks of gestation or < 1500 g birth weight.

Specific Aims and Hypotheses

Specific Aim To evaluate the association between mode of delivery and duration of second stage of labor and risk of developing IVH among singleton preterm infants born less than 30 weeks gestation or less than 1500 grams.

Hypothesis 1 Among singleton preterm infants born less than 30 weeks gestation or less than 1500 grams vaginal delivery will have an increased risk of IVH compared to cesarean delivery.

Hypothesis 2 Among singleton preterm infants born less than 30 weeks gestation or less than 1500 grams duration of second stage of labor is directly associated with risk of IVH.

Methods

Study Design and Population

To evaluate this association, we used data from Baystate Medical Center at Springfield, MA which is one of the centers of the Vermont Oxford Network (VON). The VON is a non-profit voluntary collaboration of health care professionals established in 1988 and includes over 850 Neonatal Intensive Care Units around the world (www.vtoxford.org) (179). The Baystate Medical Center database contains all the infants born at or before 30 weeks of gestation or with birth weight less than 1500 g admitted to the neonatal unit between January 2003 and August 2008 (n=631). Study exclusions included multiple gestation (n=181), transfers or congenital malformations (n=23), operative vaginal deliveries (n=6), and deaths within 48 hours (n=20) (Fig 3.3). Thus, we had a final sample (n=401) of 148 vaginal and 253 cesarean deliveries for our analysis.

Exposure Assessment

Duration of Second Stage of Labor

An Electronic Medical Record (EMR) is defined as an application environment consisting of a clinical data repository, clinical decision support, controlled medical vocabulary, order entry, computerized provider order entry, pharmacy, and clinical documentation applications (180). The EMR data entry was divided in two broad categories namely *unstructured and structured*. *Unstructured* data is comprised of free text, qualitative data and information entered by a care provider after clinical assessment. *Structured* fields are mostly quantitative, have predefined limitations, and can be queried to retrieve required data.

The information on duration of second stage of labor was obtained from the obstetric EMR and was merged with the VON database with matching identifiers (Last name, Date of Birth and Birth Weight). If the maternal record was matched with neonatal database based on only a single identifier, we reviewed the entire maternal EMR (using neonatal complications, medications, delivery times etc.) to cross-check the matching. Duration of second stage was defined as the time between complete cervical dilation (10 cm) of the cervix to the time of fetal expulsion. If the information on duration of second stage was absent in *structured* fields, we examined the *unstructured* free text from the progress notes and the discharge summary to confirm the duration values. If a 'precipitous labor' or 'rapid labor' was noted in the progress notes and the value of duration of second stage was missing in the *structured* fields we entered 1 minute as the value for duration. We also used 1 minute as a replacement for 0 minutes values in the structured fields.

Duration of second stage of labor was treated primarily as a continuous variable. For a sub-analysis we also evaluated the association of duration of second stage on IVH using the following categorization of second stage; 1) $\leq 1^{st}$ quartile vs. $> 1^{st}$ quartile, 2) $\leq$ median vs. > median 3) $\leq 3^{rd}$ quartile vs. $> 3^{rd}$ quartile.

Mode of Delivery

Information on the mode of delivery was extracted from the obstetric EMR along with the duration data. The information on the mode of delivery was entered in the EMR by trained medical professionals. This data was also merged with neonatal records from the VON database. The identifiers were deleted from the database once the merging procedure was complete. Mode of delivery was categorized primarily as vaginal and cesarean delivery. Further sub analysis was conducted using three categories namely, 1) vaginal delivery, 2) cesarean delivery with exposure to second stage and 3) cesarean without exposure to second stage.

Validity of Exposure Assessment

The information about mode of delivery and second stage of labor are entered in the hospital database by a trained medical professional. The time of complete dilation (10 cm) is entered when an obstetrical provider finds the cervix to be completely dilated during a pelvic examination. However, this may not be the exact time of complete dilation as the cervix could have been dilated for a long time before the pelvic examination and the true duration could be longer than the observed duration. In practice, the duration of second stage is measured in this manner universally. On the other hand, the exact time of delivery, which is the end point for second stage of labor is almost always measured accurately by the attending obstetrical provider.

Outcome Assessment and Validity of Outcome

Intraventricular hemorrhage was detected by cranial ultrasound performed on or before the 28th day after delivery. A cranial ultrasound was conducted at regular intervals from the 2nd day to the 28th day after delivery. The IVH grades defined as hyperechogenicity in the lateral ventricles were classified in 4 grades (127); Grade 1 is sub-ependymal hemorrhage (SEH) with no blood clot in the ventricular lumen., grade 2 is blood within the lumen without ventricular dilation, grade 3 is IVH with ventricular enlargement and grade 4 is IVH along with parenchymal hemorrhagic infarction (133). In our primary analysis we dichotomized IVH as any grade IVH (Grades 1, 2, 3, & 4) *vs.* no IVH. For a sub analysis we grouped Grade 3 and grade 4 of IVH together as severe IVH and used a dichotomized outcome as 'severe IVH (Grades 3 & 4)' *vs.* 'mild (Grades 1 & 2) or no IVH'. The diagnosis of IVH was made by a trained radiologist. A grade from 1 to 4 was assigned by the radiologist according to the severity of IVH.

Covariate Assessment

Data regarding maternal characteristics and obstetric variables were collected from the obstetric EMR. The maternal characteristics are entered in the records by a trained medical nurse and the obstetric variables are entered by the obstetrical provider. The neonatal variables were abstracted from the Baystate Medical Center's VON database. Neonatal characteristics were completed by a neonatologist.

Data Analysis Plan

Univariate Analysis

The distribution of maternal and fetal characteristics of subjects selected in the study along with duration of second stage of labor and IVH are presented as number and

percentage for categorical variables and mean and standard deviation for continuous variables (Table 3.2a and 3.2b)

Bivariate Analysis

The maternal and fetal characteristics were cross tabulated according to the exposures, mode of delivery (vaginal and cesarean delivery) (Table 3.2a and 3.2b) and dichotomized duration of second stage of labor (less than and more than median duration of second stage of labor) (Table 3.3a and 3.3b). The categorical variables were evaluated using a chi-square test and Fisher's exact test was used when cell size was not sufficient. *P* values reflecting the differences were presented for all characteristics. We used independent sample t test to determine if duration of second stage and other continuous variables such as maternal age, gestational age and birth weight varied significantly across the exposure categories.

Multivariable Analysis

Analysis was performed using multivariable logistic regression in SAS software, version 9.1© SAS Institute Inc., Cary, NC, USA. We modeled the relationship between the two exposures: 1) mode of delivery (Table 3.4) and 2) duration of second stage (Table 3.5a and 3.5b) and the two outcomes 1) IVH vs. no IVH and 2) severe IVH vs. mild or no IVH. The exposure mode of delivery was primarily used to compare the risk of IVH between vaginal and cesarean delivery. However, for the sub-analysis we compared vaginal delivery with cesarean deliveries with second stage of labor and also without second stage of labor. We also compared cesarean deliveries with second stage of labor with those without second stage of labor. The results are presented as odds ratios with 95% confidence intervals (Table 3.4).

We evaluated the association between duration of second stage of labor and IVH primarily by using it as a continuous variable and assessing the risk increase for each unit (one minute) increase in duration. We also examined the association between those with longer second stage duration compared with shorter second stage duration using quartiles as comparison categories (Table 3.5a). Similar analysis was conducted to evaluate the risk for severe IVH (Table 3.5b). With regards to second stage of labor as an exposure, we expect to observe a skewed distribution for duration of second stage of labor. Therefore, along with a multivariable logistic regression model we also analyzed its effect on IVH using linear splines at a specific knot (10 min) after evaluating the distribution of duration of second stage of labor against the predicted probability of IVH. We created two new variables (x1 and x2) from the primary predictor of duration (x) such that x1=x and x2=(x-10)| x1>10, else x2=0, where 10 is the knot value. Using x1 and x2 as predictors we interpreted the association of duration of second stage within 10 minutes and its association with IVH after 10 minutes. The results are presented as adjusted odds ratios with 95% confidence intervals (Table 3.5a and 3.5b).

We used the smallest possible Akaikes Information Criterion (AIC) for selection of best fitting model and Hosmer- Lemeshow test to check for goodness of fit along with one-step difference in Pearsons chi-square for most influential observations. To assess confounding we independently included each potential confounder in the model. In a small sample size, significance testing in a multivariable model using $P<0.05$ is more likely to delete covariates that might be important confounders (68). Therefore we used a less conservative $P < 0.2$ to select potential confounders and then using equivalence testing or 10% bias tolerance we kept variables that changed the association between mode of delivery and IVH by 10% or more in the final multivariable models. Birth

weight ratio calculated as birth weight divided by the 50th percentile of birth weight for that gestational age was assessed as a confounder in a separate analysis. However, only gestational age was a significant confounder among the covariates examined as potential confounders.

We think that the impact of second stage of labor on IVH would be affected by the level of maturity of the fetus and maternal BMI. An immature fetus and women with higher BMI would show a stronger association between labor and IVH. Gestational age and birth weight are good surrogates for fetal maturity. Interaction effect by factors such as gestational age, birth weight and BMI was assessed by using a criterion of $P_{interaction} < 0.10$ for statistical significance.

Sample Size and Power

With a sample size of 401 and a 30 % prevalence of IVH (Table 3.2a) we would have a power of 86.5% (Table 3.6).

Missing Data Analysis

We observed missing data on second stage of labor (27 out of 148 vaginal deliveries) in the data abstracted from the obstetric EMR. A comparison of obstetric and fetal characteristics was done between vaginal deliveries with missing second stage duration (n=27) and vaginal deliveries included in the study (n=121) (Table 3.7).

In a separate study examining the reasons for missing duration of second stage and comparing it with available duration, we evaluated singleton preterm vaginal deliveries between May 2001 and August 2008 at the same center. Of 1,995 records that met study criteria, the *structured* fields lacked the time at full cervical dilation in 311 charts (15.6%). This missing information was located in the *unstructured* progress notes in 44 charts (14.2% of 311). The labor of women with entries in *unstructured* fields

(n=44) had a significantly shorter second stage of labor than the women with complete structured field entries (n=1684) (13.9 ± 12.8 min vs. 36.6 ± 50.4 min; p<0.0001). The reasons for missing duration of second stage for the 311 deliveries are presented (Figure 3.2). The most common reason (56.9%) for missing data was that the pelvic examination at or before 8.5 cm dilation was the last examination before delivery. Missed 10 cm dilation on pelvic examination could probably be explained by a faster second stage of labor. The data entry error rate was 0.5% for the randomly examined charts (n=200).

Results

There were 118 (29.9%) cases of IVH in the study sample of 401 infants with vaginal deliveries having significantly higher proportion of IVH compared to cesarean deliveries (39.3% vs. 24.5%, p=0.002). However, examining the effect of mode of delivery on severe IVH (grade 3 and 4) there was no significant difference between vaginal and cesarean deliveries(6.9 % vs. 7.2%, p=0.90) in an unadjusted analysis (Table 3.2a). The majority of deliveries in our study sample were cesarean (n=253) and 5.1% (n=13) of these cesarean were conducted after second stage of labor. The mean ± standard deviation of duration of second stage for vaginal deliveries was significantly shorter compared to cesarean deliveries (13.5 ± 14.4 min vs. 22.8 ± 14.3 min, p=0.03) (Table 3.2a). Women who had cesarean delivery were more likely to be older (27.2 ± 6.2 vs. 25.6 ± 6.9 yrs, p=0.02), multiparous (58.5% vs. 48 %, p=0.04) , with a longer gestational age (28.4 vs. 27.8 weeks, p=0.04) and a lower one minute apgar score for the infant (5.1 ± 2.6 vs. 5.7 ± 2.6 , p=0.01) (Table 3.2b).

In an unadjusted analysis comparing the outcome across the median of second stage of labor in our sample we found no significant association between second stage of labor (≤ 10 min vs. > 10 min) and development of IVH (39.4% vs. 45.9 %, p=0.45) or

severe IVH defined as grade 3 or grade 4 IVH (7% vs. 11.5%, p=0.37) (Table 3.3a). There were no significant differences in the obstetric and fetal characteristics when compared across the median of duration of second stage of labor (Table 3.3b). However, those with a more than 10 minute second stage were more likely to have a male infant compared to those with less than or equal to a 10 minute duration (63.5% vs. 46.5%, p=0.048)

In multivariable analysis after adjusting for gestational age vaginal delivery was associated with increased risk for IVH compared to cesarean delivery (OR: 1.92, 95% Confidence Interval [CI]: 1.22, 3.00). However there was no significant increase in risk for severe IVH for vaginal delivery as compared to cesarean delivery (OR: 0.84, 95% CI: 0.37, 1.9) (Table 3.4). We found an increased risk of IVH associated with vaginal delivery compared to cesarean with no second stage (OR: 2.2, 95% CI: 1.39, 3.50) and to cesarean with second stage of labor (OR: 3.4, 95% CI: 0.99, 11.70). However the risk of severe IVH associated with vaginal delivery compared to cesarean and cesarean with no second stage was not significant (Table 3.4). We did find a protective effect by vaginal delivery for severe IVH (OR: 0.19, 95% CI: 0.04, 0.90) compared to cesarean delivery with second stage of labor (Table 3.4).

In a multivariable analysis adjusting for gestational age and examining the effect of duration of second stage of labor in IVH, we found no significant increase in risk for an unit increase in duration (OR: 1.01, 95% CI: 0.98, 1.03). However, using linear spline with a knot at 10 minutes the risk of IVH increased every minute by 1.15 times (95% CI: 1.03, 1.29) for the first 10 min and decreased by 0.98 times (95% CI: 0.76, 1.26) for every minute increase thereafter (Table 3.5a). Using the first quartile (3 minutes) as a cut-off we found that the risk of IVH was higher for those with duration > 3 minutes (OR:

3.81, 95% CI: 1.55, 9.31) compared to women who labored ≤ 3 min. However when compared across the median, women who labored more than 10 min had a higher risk (OR: 1.31, 95% CI: 0.65, 2.66) but this finding was non-significant (Table 3.5a). Evaluating the effect of duration of second stage on severe IVH and controlling for gestational age, we found that there was no significant association between duration of second stage and risk of IVH (Table 3.5b).

There was no significant difference in obstetric and fetal characteristics between vaginal deliveries with missing duration of second stage (n=27) and those with duration of second stage available (n=121) (Table 3.7). Although not significant, we found that vaginal deliveries with missing second stage duration were more likely to be multiparous compared to vaginal deliveries included with available second stage of labor (63% vs. 44.7%, p=0.08) (Table 3.7).

Discussion

In this retrospective study of infants weighing less than 1500 g or less than 30 weeks of gestation the risk of IVH in general was 3.8 times (95% CI: 1.55, 9.31) higher among those who had a second stage > 3 minutes compared to those with second stage ≤ 3 minutes. The increase in risk of IVH for every minute increase in second stage was only significant for the first 10 minutes (OR: 1.15, 95% CI: 1.03, 1.29) but was non-significant for those more than 10 minutes (OR: 0.98, 95% CI: 0.76, 1.26). However, we found no statistically significant association between duration of second stage and risk of severe IVH after controlling for gestational age (Table 3.5b). Evaluating the effect of exposure to second stage of labor, we found that both, ‘vaginal’ (OR: 2.20, 95% CI: 1.39, 3.50) and ‘cesarean delivery with second stage of labor’ (OR: 7.4, 95% CI: 2.19, 25.48) significantly increased the risk of IVH when compared to ‘cesarean with no second stage

of labor' (Table 3.4). The risk of severe IVH was higher among 'cesarean delivery with second stage of labor' (OR: 4.13, 95% CI: 1.01, 16.92) when compared to 'cesarean with no second stage of labor' (Table 3.4). These results suggest a potential role of second stage of labor in the development of IVH. However, the possibility of confounding by indication of cesarean delivery after second stage we suggest cautious approach in interpreting the increased risk of IVH associated with cesarean delivery after second stage.

Evaluating the effect of mode of delivery, we found that vaginal delivery resulted in an almost two fold increased risk of IVH in general when compared to cesarean delivery (OR: 1.92, 95% CI: 1.22, 3.00), however, it was not significantly associated with severe IVH (OR: 0.84, 95% CI: 0.37, 1.9). Our results are similar to previous studies which showed an increased risk for IVH by vaginal deliveries (143,150-151,181) The largest prospective study conducted by Hansen and Leviton included 1588 very low birth weight infants and found an increased risk of 1.6 times among vaginal deliveries compared to cesarean after adjusting for gestational age and antenatal steroids along with birthweight. Similarly, O'Shea *et.al* (1992) in his prospective cohort of 201 very low birth weight infants found an increased risk of IVH (RR: 2.0, 95% CI: 1.1, 3.8) for vaginal deliveries compared to cesarean when adjusted for gestational age (181). On the other hand, many studies have also found that there is no association between mode of delivery and risk of IVH (146-148, 182, 183). The recent largest population based study by Riskin *et al*. (2008) included 4658 singleton vertex presentating infants delivered between 24-34 weeks (148). The authors found a significant difference between risk of IVH among vaginal deliveries compared to Cesareans (13.6% vs.7.7% $p<0.001$) but when stratified by gestational age the risk was similar in all gestational age groups with

the adjusted OR being 0.98 (95% CI: 0.77, 1.24). A database review by Shankaran *et al*.,(1996) showed that mode of delivery was not significant in the final multivariate model for risk of grade 3 and 4 IVH in 4795 infants (149).

We excluded subjects with missing duration of second stage (n=27 out of 148) in our analysis. The obstetric and neonatal characteristics of women excluded were not significantly different from those included in our analysis. However, the significantly less number of severe IVH cases in the missing duration category (n=1) compared to those with available duration of second stage (n=9) (Table 3.7) suggests that women with shorter duration of second stage (precipitous labor) are more likely to have a missing value for second stage. This non-random missingness of the duration of second stage implies that the observed risk could be different from the expected risk because of this exclusion. This could have biased the results on either side of the null but we believe it to be minimal. We also excluded instrumental deliveries and transfers from other hospitals. The excluded deliveries may have had a different association between labor and IVH. But, we expect the bias resulting from their exclusion to be minimal as the number of transfers and the number of instrumental deliveries was minimal. Birth weight can be considered as a proxy for maturity. We used birth weight ratio calculated as birth weight divided by the 50^{th} percentile of the birth weight for that gestational age as a confounder in a separate analysis. It was found to be non-significant in the logistic model. Our results could be biased on either side of the null because of our lack of complete information on confounding factors like fetal presentation, maternal hypertensive disorders, chorioamnionitis and indication for cesarean section.

An early preterm delivery is usually presented secondary to preterm labor, prelabor premature rupture of membranes, preeclampsia, placental abruption, cervical

incompetence and fetal indications. These reasons for an early preterm delivery are grouped as uterine inflammation and placental dysfunction (184). We did not have data regarding reasons for early preterm delivery, which limited our ability to evaluate the association stratified by these reasons.

The time of complete dilation (10 cm) is entered when an obstetrical provider finds the cervix to be completely dilated during a pelvic examination. However, this may not be the exact time of complete dilation as the cervix could have been completely dilated for few minutes before the pelvic examination and the true duration could possibly be longer than the observed duration. A misclassified and inflated category of shorter duration will be independent of the outcome. Such misclassification will bias the effect towards the null and only underestimate the risk of IVH.

The newborns with IVH are in critical condition just after delivery. It is possible that the time of delivery could be entered after a significant delay because the medical staff could be involved in caring for these critical neonates. Therefore, it is possible that the duration of second stage is erroneously longer in these cases. This error, as it is dependent on the presence of the outcome variable, is a differential misclassification of the duration of second stage. This could bias the risk on either side of the null; however, we believe such bias to be minimal as the time of delivery is accurately noted by trained professional staff that is not involved with immediate neonatal care after the umbilical cord is cut. Any bias resulting from this differential misclassification on either side of the null would be negligible.

We did not find any significant association between duration of second stage and risk of IVH. However, the trend of increasing risk for IVH in the first 10 minutes of second stage and the non-significant risk after the first 10 minutes for IVH is worth future

exploration. Future studies with a larger sample size are required to help further the knowledge about the association between duration of labor and risk of IVH

Although our study sample was predominantly Caucasian women from a single center in Massachusetts, we believe that our results could be generalized to all races assuming that race and ethnicity does not significantly impact the association between labor and IVH. Our study sample received prenatal care at a tertiary medical center which means the women who missed their prenatal care or were treated at other centers were excluded. We also excluded multiple gestations and instrumental deliveries from our analysis. We may have excluded high risk cases because of these exclusion criteria and therefore may not be able to generalize our results to such cases.

Significance

A high proportion of newborns <1500 grams in weight or <30 weeks gestation suffer from IVH. With increase in survival of this vulnerable group long term morbidity remains vitally important. No previous studies have ever examined the association of duration of second stage with risk of IVH. Although the decision about mode of delivery for very small babies is multi-factorial, a non-significant risk of severe IVH after vaginal delivery or simply exposure to labor as suggested in our study provides us an opportunity for expectant management in very preterm births where cesarean delivery carries risk. Our study not only represents a significant proportion of New England periviable neonatal population but also evaluates for the first time the duration of second stage of labor as a risk factor.

Human Subjects

The study was approved by the Institutional Review Board of the Baystate Medical Center. The electronic medical records were analyzed without any identifier so

that there was no threat to the patient's privacy. Only trained personnel were allowed to access the medical charts in the hospital records room to ensure the safety of patient information.

Every effort was made to ensure that confidential information remained secure. Study personnel were trained in privacy protocols and completed questionnaires and medical records forms were kept under lock and key. Computer files were kept on a secure server that was password protected, with only study personnel able to access these files. There were no known risks to participants, with the exception of any breach of confidentiality.

Permission to Access Data

The Institutional Review Board at Baystate Medical Center approved the research proposal in May 2009 and there has been an annual renewal of this project until May 2011

Table 3.1. Characteristics of studies examining risk of developing severe IVH after vaginal delivery.

Authors (Year) & Study Design (n)	Inclusion Criteria	Subject Selection	Confounders controlled
Goepfert *et al*.(1999) Prospective (n=486)	singletons only birth weight ≤ 1000 g and gestational age > 20 weeks survived > 2 days	NICHD MFMU network of 11 centers in USA prospectively collected from 1992 to 1993	Maternal age, race, GA, PPROM, preeclampsia, IUGR, chorioamnionitis, MgSo4, birth weight,betamimetics
Paul *et al*. (2002) Retrospective (n=705)	single & multiple gestations birth weight < 1500 g	Review of a single NICU center cohort at Delaware, USA from 1993 to 1998	Maternal age, race, GA, SGA, fetal presentation, PPROM, oligohydramnios, multiple gestation, preeclampsia, inborn status
Linder *et al*. (2003) Matched Case Control (n=105)	single & multiple gestations grades 3 and 4 IVH & birth weight < 1500 g	Cases and Controls from Rabin Medical Center, Israel from 1995 to 1999	Two Controls for each case matched for GA (±1 week) and birth weight (±100 g)
Riskin *et al*. (2008) Retrospective (n= 4658)	singletons <1500 g with GA=24-34 wks	Israel's National VLBW infants database from 1995-2004	Maternal age, ethnicity, GA, PPROM, 1 min APGAR, gender chorioamnionitis, steroids, birth weight, tocolytics, contractions infertility treatment Preeclampsia, resuscitation, antepartum hemorrhage

NICHD MFMU: National Institute of Child and Human Development, Maternal Fetal Medicine Units, SGA: Small for gestational age, PPROM: Preterm premature rupture of membrane, GA: Gestational age, IUGR: Intrauterine growth restriction, NICU: Neonatal intensive care unit

Fig 3.1. Forest plot of adjusted odds ratios examining the association between vaginal delivery and severe IVH among infants less than 30 weeks gestation or weighing less than 1500 g, along with a summary odds ratio calculated using random effects model.

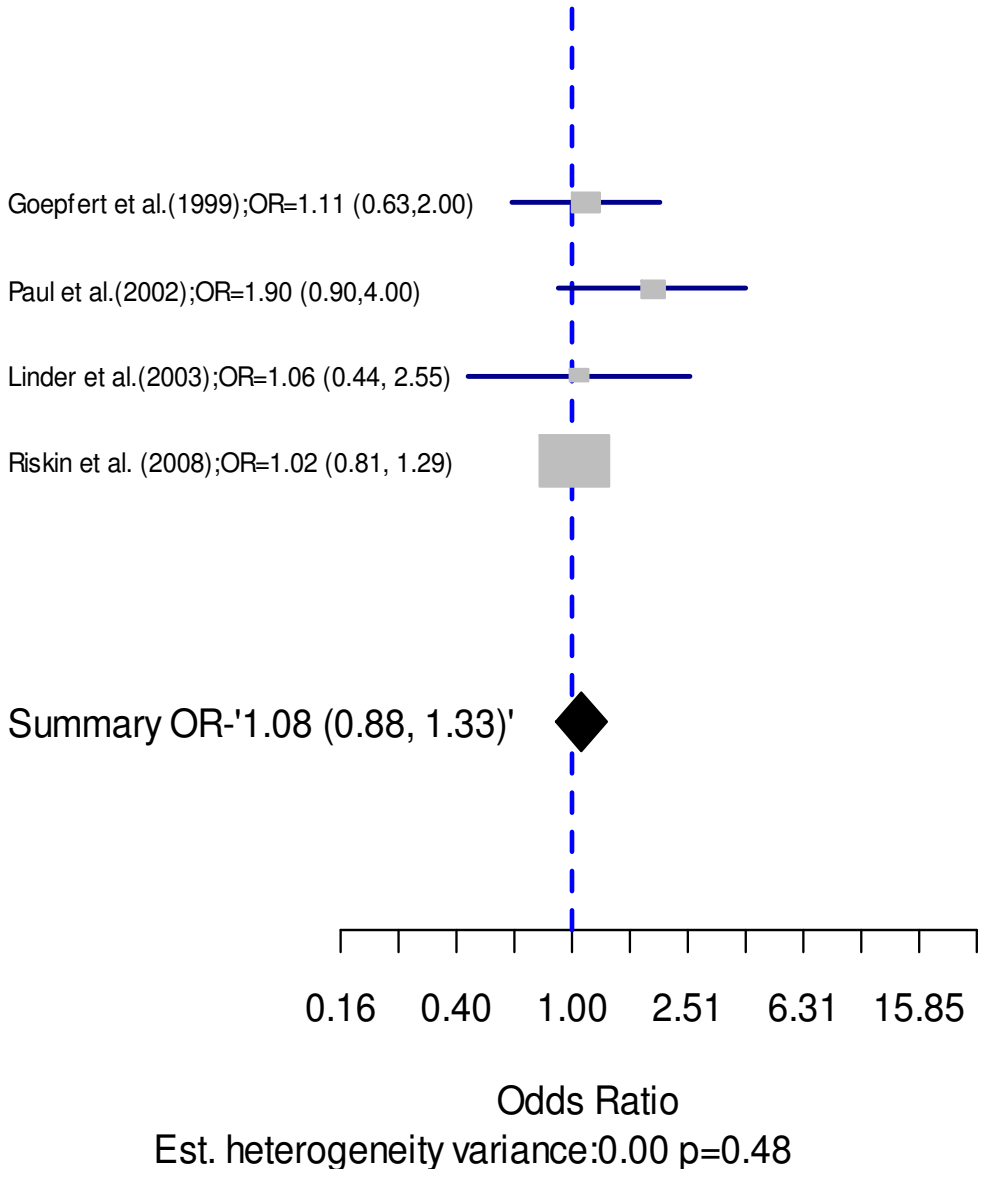
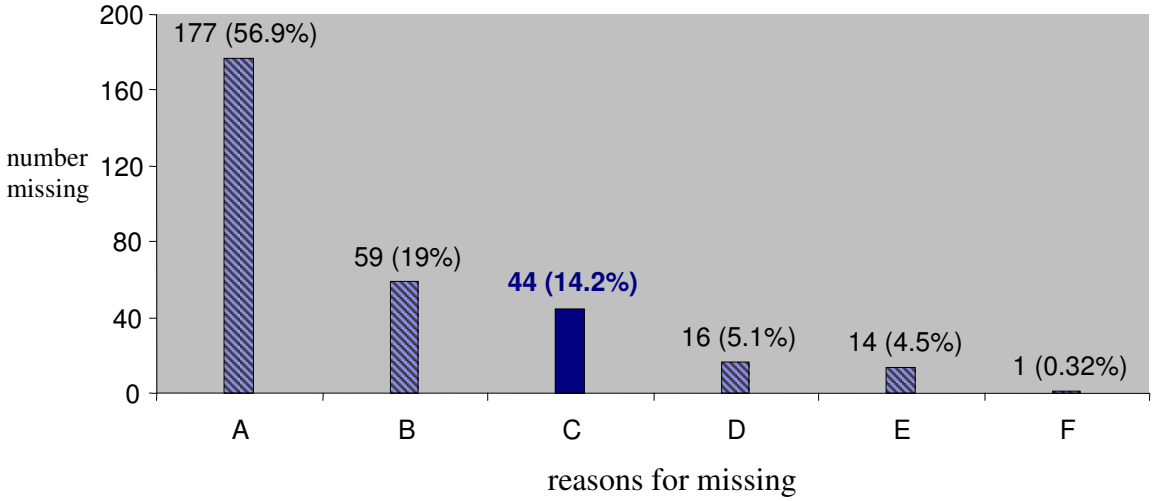


Fig 3.2. Reasons for missing values of second stage duration n=311



A : Cervical Examination with dilatation result of < 8.5 cm
B : Precipitous(very rapid) labor mentioned in progress notes
C : Failed to enter time of full dilation in structured field (missing data retrieved from unstructured fields).
D : Cervical Examination with dilation result of either 8.5, 9 or 9.5 cm.
E : Delivered at home
F : Network malfunction

Table 3.2a Distribution of duration of second stage and IVH among infants delivered before 30 weeks of gestation or birth weight < 1500 gms (n=401) stratified by mode of delivery.

	Vaginal (148)	**Cesarean (253)**	**Total (401)**	**p value***
Second stage (min)				
n	121	13	134	
mean ± S.D.	13.5 ± 14.4	22.8 ± 14.3	14.4 ± 14.6	0.03
median	9	21	10	
Second stage				
≤ 10 min	69 (57.0)	2 (15.4)	71 (53.0)	0.004
> 10 min	52 (43.0)	11 (84.6)	63 (47.0)	
Missing[@]	27	240	267	
IVH				
Grade 1	37 (25)	32 (12.6)	69 (17.2)	0.01^
Grade 2	10 (6.8)	11 (4.3)	21 (5.3)	
Grade 3	3 (2)	4 (1.6)	7 (1.7)	
Grade 4	7 (4.7)	14 (5.6)	21 (5.3)	
No IVH	88 (59.5)	188 (74.3)	276 (68.8)	
Missing	3 (2)	4 (1.6)	7 (1.7)	
IVH (any grade)				
No	88 (60.7)	188 (75.5)	276 (70.1)	0.002
Yes	57 (39.3)	61 (24.5)	118 (29.9)	
Severe IVH (3 & 4)				
No	135 (93.1)	231 (92.8)	366 (92.9)	0.90
Yes	10 (6.9)	18 (7.2)	28 (7.1)	

@ Cesarean deliveries with missing second stage duration may or may not have had second stage
**pooled t test for continuous and chi-square test for categorical variables, ^Fisher's exact test,*

Table 3.2b Distribution of obstetrics and neonatal characteristics of infants delivered before 30 weeks of gestation or birth weight < 1500 gms (n=401) stratified by mode of delivery.

	Vaginal (148)	**Cesarean (253)**	**Total (401)**	**p value***
Maternal age (years)				
mean ± S.D.	25.6 ± 6.9	27.2 ± 6.2	26.6 ± 6.5	0.02
Gestational age (weeks)				
mean ± S.D.	27.8 ± 2.8	28.4 ± 2.7	28.2 ± 2.8	0.04
Birth weight in grams				
mean ± S.D.	1078.2 ± 293.4	1063.9 ± 314.7	1069.2 ± 306.8	0.65
Parity				
Nulliparous	77 (52)	105 (41.5)	182 (45.4)	0.04
Multiparous	71 (48)	148 (58.5)	219 (54.6)	
Race				
Hispanic	49 (33.1)	84 (33.2)	133(33.17)	0.98
Non-Hispanic	99 (66.9)	169 (66.8)	268 (66.83)	
RDS				
No	86 (58.1)	155 (61.3)	241 (60.1)	0.53
Yes	62 (41.9)	98 (38.7)	160 (39.9)	
Antenatal Steroids				
No	28 (18.9)	56 (22.1)	84 (20.9)	0.44
Yes	120 (81.1)	197 (77.9)	317 (79.1)	
Continuous Ventilation				
No	58 (39.2)	87 (34.4)	145 (36.2)	0.33
Yes	90 (60.1)	166 (65.6)	256 (63.8)	
High Frequency Ventilation				
No	93 (62.8)	147 (58.1)	240 (59.8)	0.35
Yes	55 (37.2)	106 (41.9)	161 (40.2)	
Surfactant in Delivery Room				
No	89 (60.1)	156 (61.7)	245 (61.1)	0.76
Yes	59 (39.9)	97 (38.3)	156 (38.9)	
Apgar Scores				
1 minute	5.7 ± 2.6	5.1 ± 2.6	5.3 ± 2.6	0.01
5 minute	7.2 ± 2.1	6.8 ± 2.3	6.9 ± 2.2	0.17
Infant Gender				
Female	72 (48.6)	113 (44.6)	185 (46.1)	0.44
Male	76 (51.4)	140 (55.4)	216 (53.9)	

**pooled t test for continuous and chi-square test for categorical variables, ^Fisher's exact test,*

Table 3.3a Distribution of duration of second stage and IVH among infants delivered before 30 weeks of gestation or birth weight < 1500 g after experiencing second stage of labor (n=134) stratified by second stage median.

	Second stage ≤ 10 min (n=71)	**Second stage >10 min (n=63)**	**Total (n=134)**	**p value***
Mode of Delivery				
Vaginal	69 (97.2)	52 (82.5)	121 (90.3)	0.004
Cesarean	2 (2.8)	11 (17.5)	13 (9.7)	
Second stage (min)				
mean ± S.D.	4.1 ± 3.1	25.9 ± 13.9	14.4 ± 14.6	<0.0001
median	3	21	10	
IVH				
Grade 1	19 (26.7)	16 (25.4)	35 (26.1)	<0.0001^
Grade 2	4 (5.6)	5 (7.9)	9 (6.7)	
Grade 3	1 (1.4)	3 (4.7)	4 (3.0)	
Grade 4	4 (5.6)	4 (6.4)	8 (6.0)	
No IVH	43 (60.5)	33 (52.4)	76 (56.7)	
Missing	0 (0)	2 (3.1)	2 (1.5)	
IVH (any grade)				
No	43 (60.6)	33 (54.1)	76 (57.6)	0.45
Yes	28 (39.4)	28 (45.9)	56 (42.4)	
Severe IVH (grade 3 & 4)				
No	66 (93.0)	54 (88.5)	120 (90.9)	0.37
Yes	5 (7.0)	7 (11.5)	12 (9.1)	

**pooled t test for continuous and chi-square test for categorical variables, ^Fisher's exact test,*

Table 3.3b Distribution of obstetric and fetal characteristics among infants delivered before 30 weeks of gestation or birth weight < 1500 g and experiencing second stage of labor (n=134) stratified by second stage median.

	Second stage ≤ 10 min (n=71)	**Second stage >10 min (n=63)**	**Total (n=134)**	**p value***
Maternal age (years)				
mean ± S.D.	27.7 ± 7.2	25.4 ± 6.6	25.7 ± 6.7	0.25
Gestational age (weeks)				
mean ± S.D.	27.6 ± 1.8	27.8 ± 2.7	27.8 ± 2.6	0.81
Birth weight in grams				
mean ± S.D.	1139 ± 243.1	1075.4 ± 286.0	1081.6 ± 281.9	0.43
Parity				
Nulliparous	33 (46.5)	39 (61.9)	72 (53.7)	0.07
Multiparous	38 (53.5)	24 (38.1)	62 (46.3)	
Race				
Hispanic	45 (63.4)	41 (65.1)	86 (64.2)	0.83
Non-Hispanic	26 (36.6)	22 (34.9)	48 (35.8)	
RDS				
No	26 (36.6)	28 (44.4)	54 (40.3)	0.35
Yes	45 (63.4)	35 (55.6)	80 (59.7)	
Antenatal Steroids				
No	13 (18.3)	12 (19.1)	25 (18.7)	0.91
Yes	58 (81.7)	51 (80.9)	109 (81.3)	
Continuous Ventilation				
No	24 (33.8)	24 (38.1)	48 (35.8)	0.60
Yes	47 (66.2)	39 (61.9)	86 (64.2)	
High Frequency Ventilation				
No	41 (57.8)	42 (66.7)	83 (61.9)	0.28
Yes	30 (42.2)	21 (33.3)	51 (38.1)	
Surfactant in Delivery Room				
No	40 (56.3)	41 (65.1)	81 (60.4)	0.30
Yes	31 (43.7)	22 (34.9)	53 (39.6)	
Apgar Scores				
1 minute	4.4 ± 3.1	5.6 ± 2.5	5.5 ± 2.6	0.10
5 minute	6.3 ± 2.9	7.2 ± 1.9	7.2 ± 2.1	0.29
Infant Gender				
Female	38 (53.5)	23 (36.5)	61 (45.5)	0.048
Male	33 (46.5)	40 (63.5)	73 (54.5)	

**pooled t test for continuous and chi-square test for categorical variables, ^Fisher's exact test,*

@ Cesarean deliveries with missing second stage duration may or may not have had second stage

Fig 3.3 Study sample selection from Vermont Oxford Network Database

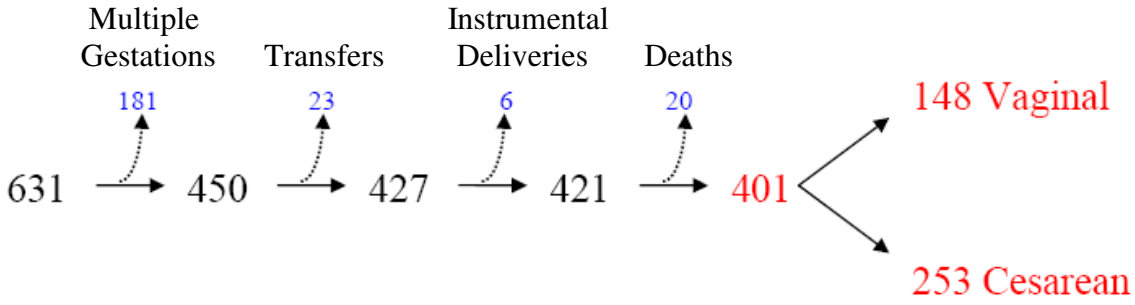


Table 3.4 The multivariate adjusted odds ratio showing association of mode of delivery with developing intra-ventricular hemorrhage among infants born before 30 weeks or with birth weight less than 1500 g

Exposure (n)	Reference (n)	IVH of *any grade* OR (95% CI)*	IVH of *grades 3 & 4* OR (95% CI)*
Vaginal (145)	All Cesarean (249)	1.92 (1.22, 3.00)	0.84 (0.37, 1.9)
Vaginal (145)	Cesarean with no second stage of labor (236)	2.20 (1.39, 3.50)	0.95 (0.41, 2.21)
Vaginal (145)	Cesarean with second stage of labor (13)	3.40 (0.99, 11.70)	0.19 (0.04, 0.90)
Cesarean with second stage of labor (13)	Cesarean with no second stage of labor (236)	7.4 (2.19, 25.48)	4.13 (1.01, 16.92)

* Both adjusted for gestational age

Table 3.5a The multivariate adjusted odds ratio showing association of duration of second stage with developing intraventricular hemorrhage (IVH) among infants born before 30 weeks or with birth weight less than 1500 g

Outcome	Exposure	Type of Exposure	adjusted for	OR (95% CI)
IVH	Duration of second stage	> 3 min vs. ≤ 3 min	gestational age	3.81 (1.55, 9.31)
IVH	Duration of second stage	> 10 min vs. ≤ 10 min	gestational age	1.31 (0.65,2.66)
IVH	Duration of second stage	> 20 min vs. ≤ 20 min	gestational age	1.14 (0.50,2.60)
IVH	Duration of second stage	continuous	gestational age	1.01 (0.98,1.03)
IVH*	Duration of second stage ≤ 10 min	continuous	gestational age	1.15 (1.03,1.29)
IVH*	Duration of second stage > 10 min	continuous	gestational age	0.98 (0.76,1.26)

** Using linear splines and a knot at 10 min the risk for IVH was assessed*

Table 3.5b The multivariate adjusted odds ratio showing association of duration of second stage with developing grade 3 & 4 or severe intraventricular hemorrhage (IVH) among infants born before 30 weeks or with birth weight less than 1500 g

Outcome	Exposure	Type of Exposure	adjusted for	OR (95% CI)
Severe IVH	Duration of second stage	> 3 min vs. ≤ 3 min	gestational age	5.36 (0.62, 46.1)
Severe IVH	Duration of second stage	> 10 min vs. ≤ 10 min	gestational age	2.08 (0.58,7.46)
Severe IVH	Duration of second stage	> 20 min vs. ≤ 20 min	gestational age	1.20 (0.28,5.02)
Severe IVH	Duration of second stage	continuous	gestational age	1.01 (0.97,1.05)
Severe IVH*	Duration of second stage ≤ 10 min	continuous	gestational age	1.16 (0.93,1.45)
Severe IVH*	Duration of second stage > 10 min	continuous	gestational age	0.85 (0.65,1.09)

** Using linear splines and a knot at 10 min the risk for IVH was assessed*

Table 3.6 The power to detect an increase in risk of IVH with increase in duration of second stage at sample size of 400 and 0.05 significance level.

N	P0*	Odds Ratio	Power
400	0.30	1.313	0.632
400	0.30	1.430	0.856
400	0.30	1.556	0.961
400	0.30	1.690	0.993
400	0.30	1.833	0.999

*P0=probability of cesarean delivery at mean duration of second stage

Table 3.7 Distribution of obstetrics and neonatal characteristics of infants delivered vaginally < 30 weeks of gestation or birth weight < 1500 g (n=148) stratified by missingness of duration of second stage of labor.

	Not missing duration (n=121)	**Missing duration (n=27)**	**p value***
IVH			
Grade 1	30 (24.8)	7 (25.9)	0.004^
Grade 2	8 (6.6)	2 (7.4)	
Grade 3	3 (2.5)	0 (0)	
Grade 4	6 (5.0)	1 (3.7)	
No IVH	72 (59.5)	16 (59.3)	
Missing	2 (1.6)	1 (3.7)	
IVH			
No	72 (59.5)	16 (59.3)	0.06^
Yes	47 (38.9)	10 (37.0)	
Missing	2 (1.6)	1 (3.7)	
Maternal age (years)			
mean ± S.D.	25.5 ± 6.6	26.2 ± 8.2	0.61
Gestational age (weeks)			
mean ± S.D.	27.8 ± 2.7	27.9 ± 3.2	0.78
Birth weight in grams			
mean ± S.D.	1075.2 ± 286.4	1091.1 ± 330.2	0.80
Parity			
Nulliparous	67 (55.3)	10 (37.0)	0.08
Multiparous	54 (44.7)	17 (63.0)	
RDS			
No	51 (42.2)	11 (40.7)	0.89
Yes	70 (57.8)	16 (59.3)	
Continuous Ventilation			
No	46 (38.0)	12 (44.4)	0.53
Yes	75 (62.0)	15 (55.6)	
Surfactant in Delivery Room			
No	72 (59.5)	17 (62.9)	0.74
Yes	49 (40.5)	10 (37.1)	
Apgar Scores			
1 minute	5.7 ± 2.6	5.1 ± 2.6	0.32
5 minute	7.2 ± 2.1	6.8 ± 2.3	0.22
Infant Gender			
Female	59 (48.7)	13 (48.1)	0.95
Male	62 (51.3)	14 (51.8)	

**pooled t test for continuous and chi-square test for categorical variables, ^Fisher's exact test,*

APPENDIX

MULTIPLE IMPUTATION

In order to explain the process of imputation and the gain in relative efficiency, let us assume *m* as the number of imputations i.e. we will have *m* imputed data sets with values filled in for missing data (108, 109). If *Q* is the parameter for which we are using imputation then assume that the point and variance estimate for i^{th} imputed dataset to be $\hat{Q}i$ and $\hat{U}i$ respectively. So, the point estimate for the parameter Q after imputation would be the average of *m* complete point estimates $\bar{Q} = \frac{1}{m}\sum_{i=1}^{m}\hat{Q}i$. Similarly, the within imputation variance would be $\bar{U} = \frac{1}{m}\sum_{i=1}^{m}\hat{U}i$. The between imputation variance B would be $\frac{1}{m-1}\sum_{i=1}^{m}(\hat{Q}i - \bar{Q})^2$. The total variance *T* associated with $\bar{Q}$ is the total variance calculated as $T = \bar{U} + (1+\frac{1}{m})B$. The statistic $(Q-\bar{Q})T^{-1/2}$ has an approximate t distribution with ν_m degrees of freedom.

The degrees of freedom $\nu_m = (m-1)\left[1+\frac{\bar{U}}{(1+m^{-1})B}\right]^2$ is dependent on *m* and the ratio $r = \frac{(1+m^{-1})B}{\bar{U}}$. This ratio *r* is called relative increase in variance due to non-response. If Q has no missing data then r and B both are zero. With a higher number of imputations *m* and a low *r* the ν_m degrees of freedom would be large and approximate normality. The relative efficiency (RE) which we quoted above to be 98% is calculated in units of variance as $RE = (1+\frac{\lambda}{m})^{-1}$ where $\hat{\lambda} = \frac{r+2/(\nu_m+3)}{r+1}$ is the fraction of missing

information on Q (109). In our case, the relative efficiency $RE = (1+\frac{\lambda}{m})^{-1}$ where λ=22.9% and m=10 can be calculated to be 97.76%.

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