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Population-Based Placental Weight Ratio Distributions and Determinants of Placental Weight Ratios

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

POPULATION-BASED PLACENTAL WEIGHT RATIO DISTRIBUTIONS AND DETERMINANTS OF PLACENTAL WEIGHT RATIOS

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ABSTRACT

The placental weight ratio (PWR) is a common proxy for the balance between fetal and placental growth, and is defined as the placental weight over the birth weight. The objectives were (1a) to establish PWR distributions by gestational age for the overall population and (1b) for small, average and large for gestational age infants and (2) to determine what pregnancy related conditions were associated with the PWR. The data were obtained using a hospital based retrospective cohort. Nonparametric quantile regression was used for the first and multinomial logistic regression for the second objective. The results show how the PWR changes across gestation. SGA infants had higher PWR's than AGA and LGA infants. The multivariable analyses showed that the majority of risk factors were associated with a PWR>90^{th} percentile. The overall curves offer population standards, and the multivariable analysis suggests that the placenta may have particular compensatory response, each with a distinct pathophysiologic mechanism, but similar PWR outcome.

Keywords: *Placenta Weight, Birth Weight, Placental Weight Ratio, Quantile Regression, Fetal Growth, Pregnancy*

CONTRIBUTIONS

This thesis contains two manuscripts each with other contributing authors. For Chapter 4, *Population-Based Placental Weight Ratio Distributions*, the order of authorship is as follows: Macdonald E, Koval J, Natale R, Regnault T, Campbell MK. For Chapter 5, *Determinants of Placental Weight Ratios*, the order of authorship is as follows: Macdonald E, Natale R, Regnault T, Koval J, Campbell MK.

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LIST OF ABBREVIATIONS

FGR Fetal Growth Restriction

SGA Small for Gestational Age

AGA Average for Gestational Age

PWR Placental Weight Ratio

LGA Large for Gestational Age

PI Ponderal Index

BMI Body Mass Index

EVT Extravillous Trophoblasts

VEGF Vascular Endothelial Growth Factor

MPP Matrix Metalloproteinases

OR Odds Ratio

QR Quantile Regression

IPD Ischemic Placental Disease

CHAPTER 1: INTRODUCTION AND OBJECTIVES

1.1 Background and Overview

Fetal Growth Restriction (FGR) is defined as a fetus that has not reached its growth potential because of genetic or environmental factors. FGR is associated with an increased risk for perinatal morbidity and mortality.[1,2] Small for gestational age (SGA) is widely used as an indicator for FGR, since FGR cannot be measured.[3]

Fetal growth depends on placental growth; the placental weight ratio (PWR) is a common proxy for the balance between fetal and placental growth. Placental weight is the most common way to characterize placental growth, and it is a summary of many dimensions of placental growth. The placental weight measurement includes the laterally expanding growth of the chorionic disc and arborization of the villous and vascular nutrient exchange surface, which is reflected in the increasing thickness of the chorionic disk. Placental weight has been found to be lower in SGA infants than in average for gestational age infants (AGA) and large for gestational age infants (LGA).[4–8]

The PWR is defined as the placental weight divided by the birth weight, and it changes across gestation as the placenta matures. The PWR decreases as gestational age increases.[9] Placental hypertrophy and reduced fetal growth have been postulated to be an adaptation to maintain placental function in pregnant women with complications such as malnutrition. If this is true, a pregnancy with impaired fetal growth, resulting in a SGA infant, should have an increased PWR compared to those infants who are AGA or LGA.[4,10] However, other factors such as timing and severity of various pregnancy complications can also alter the PWR.

Placental weight and placental weight ratio (PWR) have been found to be predictive of maternal disease, obstetric outcome, perinatal morbidity and mortality, and childhood growth and development.[11–16] While percentile curves for birth weight are available for a variety of jurisdictions and populations, percentile curves for the PWR are

not. Many conditions that could affect placental growth and the PWR, such as preeclampsia, have been minimally studied with regards to their effect on the PWR. More specifically, the effects of maternal lifestyle conditions on placental weight between different gestational age groups have yet to be studied. Mean birth weight and placental weight significantly increase from SGA to LGA infants, yet the PWR is significantly increased in SGA infants.[5–7,17,18] Placental weight has been shown to be high in comparison to birth weight when fetal nutrient or oxygen is reduced. This is believed to be a compensatory mechanism.

A high PWR is significantly correlated with short-term adverse perinatal outcomes.[19] If the pattern of placental growth is associated with differences in the efficiency of placental function, as reflected in the PWR, this may have physiological implications. Since placental weights differ between SGA, AGA and LGA infants, size distribution trajectories to determine when and how they differ across gestational ages and percentiles will be useful for both research and clinical practice.

Thompson et al.[20] created birth weight to placental weight ratio curves using the Norwegian Birth Registry with all singleton live births in Norway from January 1999 to December 2002 (n= 198, 971). These curves were a significant contribution to the literature. Moreover, no population curves to date have looked at the differences between SGA and LGA across gestational age. Searching the existing literature we found only one additional set of PWR percentile curves in a Canadian population.[9] However, the sample size is small (n=20,309). Finally, previous studies that have looked at atypical PWRs have not used a population standard to identify abnormal PWRs.[17,21,22]

1.2 Objectives

This thesis consists of two distinct, yet highly dependent investigations. Both objectives were addressed using data from the perinatal database in London, Ontario. The specific objectives are outlined below. Objective 1a and 1b are addressed in this thesis as

one investigation and objective 2 as another. Therefore, they are presented separately in the later chapters.

Objective 1:

a. To establish placental weight ratios (PWR) distributions by gestational age in a Canadian sample.
b. To investigate whether the PWR distributions varies by fetal growth adequacy, thus stratifying the PWR distributions by fetal size: SGA, AGA, & LGA.

Objective 2:

To determine what pregnancy related conditions and lifestyle behaviours are associated with the PWR.

1.3 Structure of Thesis Document

In accordance with the standards outlined by Western University School of Graduate and Postdoctoral Studies, this thesis is presented in the integrated-article format. A comprehensive overview of the related literature and the methods common to both investigations is covered in Chapters 2 and 3, respectively. The work comprising the specific investigations is presented as two manuscripts. Chapter 4, *Population-Based Placental Weight Ratio Distribution Curves*, addresses Objective 1a) and 1b), as outlined above, while Chapter 5, *Determinants of Placental Weight Ratios,* examines Objectives 2), also outlined above. Lastly, Chapter 6, *Integrated Discussion*, summarizes the main findings of this thesis and their relationship to one another.

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CHAPTER 2: LITERATURE REVIEW

2.0 Overview

Fetal Growth Restriction (FGR) is defined as a fetus that has not reached its growth potential because of genetic or environmental factors.[1] Small for gestational age (SGA) is widely used as an indicator for FGR, since FGR cannot be measured. Fetal growth depends on placental growth; the placental weight ratio (PWR) is a common proxy for the balance between fetal and placental growth. The PWR is defined as the weight of the placenta divided by the birth weight. Placental weight has been found to differ between SGA, average for gestational age infants (AGA) and large for gestational age infants (LGA).[2–6] Many conditions that could affect placental growth and the PWR have been minimally studied with regards to their effect on the PWR. A list of definitions relevant to this chapter can be found in Appendix A.

2.1. Small for Gestational Age Infants

2.1.1. Fetal Growth Restriction and Small for Gestational Age

Fetal growth restriction (FGR) is a term used to define a fetus who has not met its growth potential because of genetic or environmental factors. SGA is widely used as a statistical indicator of FGR, since FGR is not measurable. The most common definition of SGA refers to an infant that weighs less than the 10th percentile for their gestational age and sex, as defined by the World Health Organization in the International Classification of Diseases Version 10, as per code P05.1.[7] However, this definition does not distinguish between those who are constitutionally small and those who are growth restricted.

From 1995 to 2004, the rate of SGA, relative to a fixed population standard, decreased among singleton births in Canada. This may be due to the increase in maternal size prior to pregnancy and weight gain during pregnancy, reduced cigarette smoking, changes in sociodemographic factors,[8] as well as more frequent use of ultrasound assisted dating.[9] Therefore, the prevalence of SGA in the Canadian population is currently

estimated to be 7.2% in infants born after 37 weeks gestation, 6.5% in infants between 34 and 36 weeks gestation, and 11.5% in infants born before 33 weeks gestation.[8] The incidence of SGA varies among populations and increases with decreasing gestational age.

Anthropometric data from infants born at different gestational ages have been used to generate a multitude of cross-sectional growth curves, however they are inconsistent and vary at each gestational ages based on differences in maternal characteristics and inaccurate measurements of body size and estimates of gestational age.[10,11] The majority of the literature surrounding fetal growth suffers from one or more methodological problems including errors in reporting gestational age using last menstrual period, biologically implausible birth weights for gestational age, insufficient sample sizes at low gestational age, non-generalizable samples,[12–15] and inadequate statistical modeling techniques such as a lack of smoothing of distribution curves.[16,17] Therefore, Kramer et al.[18] created sex specific birth weight distributions using the Canadian national linked file of singleton births and infant deaths for births between 1994 and 1996, for which gestational age is based mostly on early ultrasound estimates. The reference is based on singletons with gestational ages between 22 and 43 weeks and comprises 347,570 males and 329,035 females. Kramer et al.[18] assumed a normal distribution for birth weight at each gestational age and used the expectation-maximization algorithm to exclude infants with gestational ages that were more consistent with 40-week births than with the recorded gestational age. Distributions of birth weight at the corrected gestational ages were then statistically smoothed. The means and standard deviations were also tabulated to allow calculation of *z* scores in addition to percentiles.[18]

The categorization into male and female specific curves is ideal because males weigh more than females at each gestational age.[18] However, in preterm births, the average estimated fetal weight is greater than the average weight of term infants because more SGA infants are born prematurely compared to AGA infants. Therefore, estimated

fetal weight growth curves will classify more infants as SGA than birth weight gestational standards.[19]

2.1.2. Risk Factors for SGA

There are many risk factors for SGA infants which will be individually discussed in more detail below. A conceptual model indicating the risk factors for SGA infants, a decreased placental weight, and those covariates which are risk factors for both can be found in Appendix C. Also, a table showing which risk factors increase or decrease the placental weight, and are associated with either SGA or LGA, can be found in Appendix F.

2.1.2.1. Maternal Height

Maternal height has a proven positive association with infant birth weight. In a large study of births from the Swedish Birth Register between 1992 and 2001, women were categorized based on height into the following categories: <160cm, between 160cm and 170cm, and >170cm. Birth weights decreased slightly but monotonically with decreases in maternal height.[20] Kramer et al.[21] have also demonstrated that low maternal height is a risk factor for decreased birth weight in a meta analysis using effect magnitudes weighted for sample size.[21] Therefore, it has been shown that SGA rates are inversely proportional to maternal height.[22]

2.1.2.2. Maternal Weight and Pregnancy Weight Gain

An association has been elucidated between pre-pregnancy weight and birth weight. SGA rates are inversely proportional to maternal weight and a higher proportion of neonates of small and light mothers were found to be SGA.[22,23] Many studies have found an association between pregnancy weight gain and infant birth weight. Maternal weight at birth, pre-pregnancy weight and weight gain during pregnancy have been found to be responsible for 10% of the variance in fetal weight.[24] A low pregnancy weight gain

is associated with a lower birth weight based on gestational age, despite various methods of characterizing gestational weight gain. Also, mothers who were underweight before pregnancy were more likely to deliver infants of a lower weight.[25] Variations across studies in exposure categories, outcome measures, and timing of measurement prevented calculation of summary measures in a recent systematic review,[26,27] yet there was strong evidence to support associations between inadequate gestational weight gain and decreased birth weight and fetal growth (SGA).[28,29] Therefore, an infant's birth weight has clear associations with both a woman's pre-pregnancy weight and pregnancy weight gain.

2.1.2.3. Nutritional Deprivation

Although it is not seen as a major problem in developed countries, severe maternal deprivation during pregnancy can have a major impact on birth weight. During the Dutch famine of 1944 to 1945, the mean caloric intake fell from 750 to 450 kilocalories per day, and correspondingly, the average infant birth weight fell 250 grams. Also, during the World War II German siege, Leningrad suffered from a period of prolonged starvation, more so than the Dutch Famine, with a diet of nearly no protein which caused the average birth weight to fall 500 grams during this period.[30]

Modest degrees of nutrition deprivation also have an effect on birth weight. This measure is typically captured through pre-pregnancy weight and pregnancy weight gain.[24] Furthermore, celiac disease, which is marked by malabsortion of nutrients, has also been associated with FGR.[31] Markers of nutritional deprivation associated with lower fetal growth include low weight gain during pregnancy,[32] inadequate daily calorie intake, protein deficiency,[33,34] and assorted micronutrient deficiencies including calcium,[33] iron,[35,36] folate, [35–37] and zinc.[38] In developing countries, nutritional deprivation is the major source of SGA infants,[39] but less of a concern in developed countries where malnutrition is uncommon.

2.1.2.4. Exercise during Pregnancy

The evidence on the effect of exercise during pregnancy on fetal growth depends not only on the type of exercise, but also on the timing of the exercise during pregnancy. A study by our research group found that exercising five or more times a week during pregnancy was associated with reduced fetal growth.[40] Another study indicated that vigorous exercise, defined as being out of breath or heavily breathing, was associated with an approximate three-fold increase in SGA.[41,42] These results are congruent with previous research that shows that high intensity exercise is associated with reduced fetal birth weight. This is possibly mediated by reduced uterine blood flow.[43]

In a Cochrane Review by Kramer et al.[44] no effect was found on the risk of delivering a SGA infant in women who were sedentary and then increased aerobic exercise during pregnancy. Also, in women who were sedentary and then increased aerobic exercise, a 49.49g mean difference was found in birth weight when compared with controls. However, the difference was not significant. Also, when there was a reduction in exercise in physically fit women birth weight decreased by 151g, but again the difference was not significant. Increase, then reduction in exercise in physically fit women had a significant increase in birth weight by 460g compared to women who maintained their level of aerobic exercise. Reduction, then increase in exercise in physically fit women resulted in a significant decrease in mean birth weight when compared to women who maintained the same level of aerobic exercise. Increase in exercise in overweight women resulted in a small (5g), but significant reduction in birth weight when compared to controls.

On the other hand, Clapp et al.[45] found that when women began regular, moderate-intensity weight bearing exercise in early pregnancy their offspring were significantly heavier compared to controls who did not exercise. The difference in birth weight was the result of an increase in both lean body mass and fat mass.[45] Furthermore, another study by Clapp et al.[46] found that the offspring of the women who were randomly assigned to a high volume of exercise in mid and late pregnancy were significantly lighter

(3.39 kg vs 3.81 kg) and thinner (8.3% fat vs 12.1% fat) than those offspring born of women who were randomly assigned to reduce their exercise volume after the 20th week.

2.1.2.5. Parity

Parity is associated with an increased risk of delivering a SGA infant. The growth rate of the fetus of primaparous women is lower than that of multiparous women. When based on a single population standard for SGA, primiparae had significantly higher rates of SGA at all gestational ages. However, when SGA was defined based on parity specific standards, primiparae did not have higher SGA rates than multiparae after 37 weeks.[47]

2.1.2.6. Interpregnancy Interval

A short interpregnancy interval has been associated with low birth weight and FGR. This association may be mediated through depletion in folic acid.[48] The odds ratio for SGA was statistically significant, and progressively increased, as the interpregnancy interval shortened from 18 months to 6 months.[49] However, a long interpregnancy interval has also been associated with SGA infants. Interpregnancy interval longer than 60 months is also associated with a risk of delivering an SGA infant or an infant with low birth weight, defined as weight below 2500 grams.[49]

2.1.2.7. Maternal Age

FGR is the most common among pregnancies at both extremes of reproductive bearing age.[50,51]

2.1.2.8. Emotional Distress

The literature is divided on whether psychosocial stress is a risk factor for SGA, yet the evidence for psychosocial stress as a risk factor is more convincing. It has been shown that infant birth weight depends on the mother's mood during pregnancy. High

levels of anxiety and depression during pregnancy influence the infant's development through biological mechanisms of stress that include: prolonged exposure to corticotrophin-releasing hormone, brief periods of exposure to glucocorticoids, and decreased availability of substrate to the fetus. As a result, the infant is born smaller.[52,53] The evidence arguing for a relationship between psychosocial stresses and SGA is more persuasive. In contrast, in a cohort of more than 70,000 pregnant women in Norway, the association between emotional distress during pregnancy and delivering a SGA infant was estimated, after adjustment for a number of factors known to be associated SGA to be non-significant with an adjusted OR of 1.6.[54]

Emotional distress activates the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, which increases the secretion of corticotrophin-releasing hormones.[55] Elevated levels of corticotrophin-releasing hormone have been found to be associated with intrauterine growth restriction and preterm birth.[56,57]

2.1.2.9. Smoking

Cigarette smoking during pregnancy is well established within the literature as a cause of fetal growth restriction.[1,21,26,58,59] Smokers have an increased risk of having a SGA baby with relative risks ranging from 1.3 to 10.0.[60–62]

A retrospective cohort study of 13,661 deliveries, which adjusted for confounding variables of smoking including parity, age, ethnicity and BMI, found that the adjusted odds ratio of smoking for the occurrence of growth restriction was 1.9 and that, if causal, smoking accounted for 13.9% of SGA infants. Furthermore, progressive levels of cigarette consumption resulted in a greater risk of growth restriction. A dose response relationship, therefore, has been demonstrated between cigarette smoking during pregnancy and growth restriction of the infant.[63] Fetal growth may no longer be restricted once smoking ceases depending on when the smoking cessation occurs in the pregnancy.[24,64] Results from observational studies show that if the mother stops smoking during the first trimester then the rates of SGA are similar to that of non-smokers.[65] Also,

other studies indicate that if mothers stop smoking before the third trimester then the rate of SGA is similar to that of non-smokers.[61,64,66]

Smoking is hypothesized to affect birth weight through a number of different mechanisms. First, the carbon monoxide inhaled from the cigarette deprives both the fetus and the placenta of oxygen, which creates hypoxic conditions for the fetus by allowing carbon monoxide to bind to maternal haemoglobin in place of oxygen. Second, carcinogens cross the placenta and further inhibit fetal growth. Nicotine also acts as an appetite suppressant, which may lead to uterine vasoconstriction.[21]

2.1.2.10. Alcohol Consumption

A recent meta-analysis that included thirty-six case studies and cohort studies between January 1980 and August 2009 examined the effect of maternal alcohol exposure on the risk of low birth weight and SGA. The findings indicated that the overall dose–response relationship for low birth weight and SGA showed no effect up to 10g of pure alcohol/day (an average of about 1 drink/day), but with level of alcohol exposure above 10g of pure alcohol/day the relationship showed a monotonically increasing risk for both low birth weight and SGA. Therefore, the dose-response relationship indicates that heavy alcohol consumption during pregnancy increases the risks of SGA whereas light to moderate alcohol consumption shows no effect on fetal growth.[67] Results from previous studies have agreed with Patra et al's findings, but lacked large enough sample sizes to make generalizable conclusions.[1,68]

2.1.2.11. Toxins from Medications

Exposure to medications including warafin, anticonvulsants, antineoplastic agents and folic acid antagonists have been shown to result in FGR infants.[69,70] Evidence regarding the effect of anti-hypertensive medications during pregnancy on the growth of the fetus is divided. One recent systematic review found that taking anti-hypertensive medications for mild to moderate hypertension did not increase the frequency of

delivering an SGA infant.[71] However, another meta-analysis showed that fetal growth was significantly impaired by the reduction in mean arterial pressure induced by antihypertensive therapy. They found that a 10 mmHg fall in mean arterial pressure was associated with a 176 g decrease in birth weight. This effect was unrelated to the type of hypertension or choice of medication.[72]

Results of epidemiological studies examining the effect of maternal caffeine consumption on the risk of low birth weight or an SGA infant are conflicting. Several studies observed that maternal caffeine intake ranging from 200 to 400 mg per day was associated with a mean decrease in birth weight of about 100 grams,[73,74] while other studies either were not able to show any significant association with birth weight or demonstrated reduction in mean birth weight only at caffeine intake exceeding 600 mg per day.[75–77] Many of the available epidemiologic studies have been criticized for inadequately controlling for important risk factors for low birth weight, particularly smoking. However, one well-designed large prospective study assessed caffeine consumption from all known sources, objectively quantified intake, and adjusted for smoking and alcohol use. This study found that mean caffeine consumption >200 mg/day over the course of pregnancy was associated with reduction in birth weight of 60 to 70 grams. Also, the risk of FGR increased linearly in a dose-response relationship, with no plateau, yielding odds ratios of 1.2 to 1.5 compared to women who consumed less than 100 mg caffeine per day.[78] Another prospective cohort found that compared with mothers who consumed fewer than two cups of coffee per day, the adjusted odds ratios of delivering an SGA infant for mothers who consumed two to three, four to five, and six or more cups of coffee per day were 1.38, 1.50, and 1.87, ($P < 0.01$).[79]

2.1.2.12. Chronic Hypertension

Cardiovascular disease, high blood pressure, and chronic hypertension have all been linked to low birth weight.[80] Chronic hypertension is also associated with an increased risk of many vascular disorders of pregnancy, including preeclampsia and

pregnancy induced hypertension, which are also strongly associated with reductions in birth weight.[81]

Chronic hypertension is shown to exert its effects differently on both term and preterm infants. A study by Catov et al.[82], that adjusted for potential confounders, found that chronic hypertension was associated with a 5.5-fold increased risk for preterm SGA. The cause of this may involve an inadequate vascular response to pregnancy associated with abnormal placentation and may represent a pathogenesis distinct from that leading to term SGA. It has also been reported that chronic hypertension presented a 3.4-fold increase in risk of preeclampsia among nulliparous women and a 5.4 fold increase of preterm preeclampsia. Together, these results indicate a strong and convincing relationship between chronic hypertension and risk for both preeclampsia and SGA, especially for the more severe subtypes of each condition.[82]

2.1.2.13. Gestational Hypertension

Pregnancy outcomes of patients with mild gestational hypertension are generally favorable. The mean birth weight and rates of fetal growth restriction are similar to those without gestational hypertension.[83,84]

However, pregnancies with severe gestational hypertension have increased rates of SGA infants. These rates are significantly higher than the rates in the general obstetrical population without gestational hypertension and similar to rates reported for women with severe preeclampsia.[83,85,86] A study by Buchbinder et al.[83] compared outcomes in women who developed severe gestational hypertension with women who stayed normotensive or developed mild gestational hypertension or mild preeclampsia. They found that the rate of delivery of SGA infants was 20.8 and 6.5 to 4.8 percent, respectively for the 3 groups mentioned above. Since there were only 24 patients with severe gestational hypertension, this small sample limits the interpretation of these results.

2.1.2.14. Preeclampsia

Women with preeclampsia are more likely to deliver a SGA infant than in women without preeclampsia.[87]

In preeclampsia, cytotrophoblast cells penetrate the decidual portion of the spiral arteries, but fail to infiltrate the myometrial segment.[88,89] The spiral arteries do not succeed in developing into large, tortuous vascular channels. Instead of developing normally, the vessels stay narrow, which results in placental hypoperfusion and potential fetal asphyxia. This defect has been associated with preeclampsia with or without FGR, FGR without maternal hypertension as well as second trimester fetal death, placental infarcts, placental abruption, premature rupture of membranes, and preterm labor.[90] Environmental, immunological, and genetic factors all appear to play a role in this process.[91]

Preeclampsia is an etiologically diverse disorder that occurs in two subsets: one with normal or enhanced placental function and another with placental dysfunction and fetal growth restriction, which often occurs with asymmetric fetal body proportion. A study has established that in newborns of women with preeclampsia, mean birth weight, and ponderal index (PI) were lower than in women without preeclampsia.[92] Early-onset preeclampsia, defined as onset <34 weeks, is associated with placental vascular lesions and reduced uteroplacental blood supply, leading to reduced birth weight. As a result, preeclampsia and FGR in general might share a pathophysiologic mechanism.[93,94] The pathophysiology of early-onset preeclampsia differs from late onset disease in terms of neutrophil function and cytokine levels.[95]

Birth weight in preterm preeclampsia is substantially lower than in term preeclampsia.[96–98] This may be due in part to the fact that SGA infants are overrepresented in preterm preeclampsia. However, in term preeclampsia, both SGA and LGA offspring appear to be over-represented compared to the distribution in women without preeclampsia, yet mean birth weight does not differ greatly from that of

normotensive pregnancies.[97] The increase in LGA infants may possibly be related to greater placental perfusion due to elevated cardiac output and blood pressure.[92,99]

2.1.2.15. Residing at High Altitude

Living at a high altitude is associated with preplacental hypoxia and in turn a lower birth weight. A direct relationship between increasing altitude and lower birth weight was established in Denver, Colorado, Tibet and Peru.[100–102] A study in Peru that looked at the relationship between women living at different elevations and birth weight established that for each 500 meter increase in altitude above 2000 meters birth weight decreased 65 grams.[101] This association may be due to the lower cardiac output of women living at higher altitudes.[103]

2.1.3. Fetal Growth Restriction and Placental Weight

Placental weight has been shown to be directly correlated and associated with birth weight.[3–5,104] A higher proportion of SGA infants have placenta weights in the lowest 10th percentile of placental weights than LGA and AGA infants. Also, SGA infants have a lower number of placenta's with weights above the 10th percentile than both AGA and LGA infants.[105]

2.2. Excess Fetal Growth and Large for Gestational Age

Measures of LGA typically include comparison of birth weight to the birth weight distribution of another similar population, which will be used to determine LGA status in this thesis. The most common definition of LGA refers to an infant that weighs greater than the 10th percentile for gestational age and sex.[7,18]

2.2.1. Risk Factors for LGA

LGA infants can be constitutionally large because of genetic factors. In addition, a variety of maternal conditions, pregnancy complications, or fetal abnormalities can result in increased growth. Some of the main risk factors for LGA such as obesity and gestational diabetes have both been associated with poor pregnancy outcomes including excess fetal growth, increased rates of caesarean section, higher incidences of shoulder dystocia, congenital malformations, heart problems, hyperbilirubinemia, and hypoglycaemia at delivery.[106–109]

A conceptual model indicating the risk factors for LGA infants, an increased placental weight, and those covariates which are risk factors for both can be found in Appendix D. Also, a table showing which risk factors increase or decrease the placental weight and are associated with either SGA or LGA can be found in appendix F.

2.2.1.1. Pre-Pregnancy Obesity

Studies have looked at maternal obesity's effect on excess fetal growth, regardless of maternal glucose tolerance, and have found that obesity is associated with excess fetal growth. [110–112] Obese women with insulin resistance and hyperglycaemia are at a higher risk for delivering LGA infants. Obese women with normal glucose tolerance tests also have an increased risk for delivering an infant that has excessive fetal growth.[113]

2.2.1.2. Gestational Diabetes

Increased risk of excess fetal growth has been associated with gestational diabetes, especially when the diabetes is poorly controlled.[113,114,115] In gestational diabetes, the beta-cells are not capable of compensating for the increased insulin demand, and hyperglycemia develops.[109] During gestational diabetes, the level of diabetes control by the woman determines the level of risk for excess fetal growth. In pregnancies complicated by gestational diabetes, poor glycemic control is more likely to result in a LGA infant than in those pregnancies with good glycemic control.[113,115,116] High levels of

fetal insulin lead to excess fetal growth due to the subsequently high levels of growth hormones, because of the storage of excess glucose.[109]

The mechanism involves excessive delivery of nutrients to the fetus, resulting in fetal hyperglycemia, hyperinsulinemia, and increased growth, particularly of insulin-sensitive tissues such as the liver, muscles, and subcutaneous fat.[117,118] The risk of developing gestational diabetes is higher in obese women than in women of normal weight; both obesity and gestational diabetes, however, add independently to the risk of excess fetal growth.[108]

2.2.1.3. Maternal Weight Gain

Pregnancy weight gain has continually been shown to be associated with infant birth weight. Excess weight gain during pregnancy has been associated with both insulin resistance and higher birth weight infants.[119] Literature consistently shows that higher weight gains during pregnancy increase the risk of delivering a LGA infant.[120,121] Only about 35% of women actually gain the weight recommended by Institute of Medicine (IOM) guidelines[122] for all BMI categories. About 22% of women gain less weight than is recommended for their pre-pregnancy weight, and 43% gain more. As maternal pre-pregnancy BMI increases, the correlation with infant birth weight weakens. For obese women, there is no correlation between their weight gain during pregnancy and the infant's birth weight.[122] Obese women have large infants regardless of how much weight they gain during pregnancy.

2.2.1.4. Obesity, Pre-PregnancyWeight and Pregnancy Weight Gain

When women have gestational diabetes, are obese pre-pregnancy and exceed recommendations for pregnancy weight gain there is an increased risk of excess fetal growth above that which would be expected from gestational diabetes alone.[108] Therefore, while obesity and excess weight gain during pregnancy have similar pathophysiologies and adverse pregnancy outcomes, they act in distinct ways. In

pregnancies complicated by gestational diabetes an LGA infant can result even when weight gain targets are achieved and not exceeded during pregnancy.[108]

2.2.1.5. Pregnancy Nutrient and Diet

Maternal nutrition, defined by the mother's diet, has an impact on the environmental conditions experienced by the growing fetus. The specific effects of maternal nutrition on the fetus depend on both the quality of the maternal diet and the point at which nutrition was measured during pregnancy.[123] The effects of malnutrition differ depending upon the timing during gestation of the deprivation. If severe macronutrient deprivation occurs during early pregnancy, infant birth weight is not affected, but placental weight increases as described earlier. In contrast, macronutrient deprivation during the last trimester of pregnancy results in both reduced placental weights and reduced birth weights, as mentioned previously.[124]

2.2.1.6. Parity

Macrosomia occurs more often at higher parities. In a study using birth certificate data, the proportion of infants with birth weights greater than 4500 g was significantly greater as parity increased from one to six or more.[125] In another report, birth weight typically increased from 80 to 120 g in each successive pregnancy up to five.[126]

2.2.1.7. Sex

Male infants weigh more than female infants throughout gestation; as a result, more macrosomic infants are male. In one report, males were more likely than females to have increased birth weights.[125,127]

2.2.2. Excess Fetal Growth and Placental Weight

Placental weight has been shown to be directly correlated and associated with birth weight.[3–5,104] A higher proportion of LGA infants have placenta weights in the highest 10th percentile than SGA and AGA infants. Also, LGA infants have a lower number of placenta's with weights below the 10th percentile than both AGA and SGA infants.[105] Furthermore, LGA infants have been found to have lower PWRs than SGA and AGA infants.[128]

2.3. The Placenta

2.3.1. Structure and Formation of the Placenta

The placenta is a fetal organ that consists of an umbilical cord, membranes and parenchyma. Many maternal and fetal disorders may begin with the placenta, since the interface between the mother and the infant occurs at the placenta. Therefore, examination of the placenta may provide information on the impact of maternal disorders on fetal growth restriction.[129] The development of the placenta is a highly regulated process. The placenta serves various roles throughout a pregnancy including preventing the rejection of the fetal allograft, enabling gas exchange, transporting nutrients, eliminating fetal waste and secreting peptide and steroid hormones.[129]

The development of the placenta is a continuous process that begins at the time of fertilization. The first three days of development occur in the fallopian tube and on the fourth day the morula enters the uterus. By the 6th day post fertilization, the blastocyst implants in the uterine lining, typically in the upper anterior or posterior wall of the uterus. By the 13th day after fertilization, the trophoblast erodes deeper in the deciduas and forms the lacunae. The lacunae then becomes the intervillous space. The progenitor villous trophoblast cells proliferate throughout gestation and differentiate along two pathways to form either extravillous trophoblast (EVT) or syncytiotrophoblast. EVT that invades decidua is the interstitial EVT and EVT that invades and remodels the spiral arteries is the endovascular EVT.[129]

2.3.2. Characterization of Placental Growth

Placental weight is the most common way to characterize placental growth and it is a summary of many dimensions of placental growth. The placental weight measurement encompasses the laterally expanding growth of the chorionic disc and arborization of the villous and vascular nutrient exchange surface, which is reflected in the increasing thickness of the chorionic disk.[130] The average human placental weight varies between studies ranging from 438g to 680g.[3,104,131,132]

The expansion of the chorionic plate, beginning early in pregnancy, is the principle determinant of the ability of the placenta to translate its mass into birth weight.[130] As chorionic disk area and thickness increase, birth weight and placental weight also increase and the PWR increased after they adjusted for gestational age, parity, race, and infant gender.[133]

2.3.3. The Placental Weight Ratio

The PWR, the ratio of placental weight to birth weight, changes across gestation as the placenta matures. If the pattern of placental growth is associated with differences in the efficiency of placental function as reflected in the PWR, then the PWR has both physiologic and functional implications.[130] When PWRs are compared between AGA and SGA infants based on gestational age, SGA infants are found to have higher ratios than AGA infants.[2,134] This occurs since the ratio decreases with gestational age, so when fetal weight increases the ratio decreases.[2]

The placenta has been shown to have a functional reserve capacity, but there is still a higher PWR, defined as less than the 10th percentile, in SGA infants. Therefore, the PWR may be a better indication of SGA fetuses than placental weight alone.[135] The PWR has been found to be predictive of maternal disease, obstetric outcome, perinatal morbidity and mortality and childhood growth and development. A high PWR was associated with increased risk of the aforementioned.[136–141]

2.3.4. The Placenta and Fetal Growth

2.3.4.1. The Role of Placental Function and Fetal Growth Restriction

The adequate transfer of oxygen to the fetus is dependent on both the development of the uteroplacental and fetal placental circulations. Therefore, three categories of fetal hypoxia have been proposed to explain the effect of the placental function on both fetal and placental growth. The three categories: preplacental hypoxia, uteroplacental hypoxia and post placental hypoxia are described in detail below.[142,143]

2.3.4.1.1. Preplacental Hypoxia

Preplacental hypoxia is when the placenta and fetus become hypoxic because of reduced oxygen content within maternal blood, such as a pregnancy at high altitude, smoking[144] and maternal anaemia. These conditions result in reduced intraplacental oxygen content, predominately branching angiogenesis and reduced vascular impedance. Interestingly, all of these complications are associated with excessive placental weight.[142]

Pregnancies at high altitude results in increased capillary volume fraction[145–147] and increased capillary branching.[148] The density of villous cytotrophoblasts is increased.[142] Similar findings occur in pregnancies complicated by maternal anaemia. Endothelial proliferation is increased, resulting in excessive branching angiogenesis, and decreased mean capillary diameter,[149] but an increased capillary volume fraction.[150] Consequently, the placenta maintains oxygen transfer through a thinning of the placental barrier.[151] Also, the proliferation of the villous cytotrophoblast decreases as the severity of the disease increases.[149]

All of the conditions listed above are representative of typical cases of placental adaptation to preplacental hypoxia. Hypoxia affects the entire organ, since the origin of hypoxia is located before the placenta. A conceptual model showing these proposed pathways can be found in appendix G.

2.3.4.1.2. Uteroplacental Hypoxia

Uteroplacental hypoxia is when normally oxygenated maternal blood has restricted entry into the uteroplacental tissues due to either occlusion or failed trophoblast invasion of the uteroplacental arterioles. This situation represents late onset FGR with preserved end diastolic flow volume, and term preeclampsia. This condition results in reduced intraplacental oxygen content, predominately branching angiogenesis and reduced vascular impedance.[142,143]

A variety of pathways can cause restricted access of normally oxygenated maternal blood into the uteroplacental tissues. These pathways include: damage to the endothelium,[152] focal villous placental ischemia and infarction,[153] and release of proinflammatory cytokines, interleukins 6 and 8.[154] More detailed mechanisms can be found in a conceptual model in appendix H.

2.3.4.1.3. Postplacental Hypoxia

Postplacental hypoxia occurs when normally oxygenated blood enters the intervillous space, either at normal or reduced rate, but there is a defect in the fetoplacental perfusion. This defect prevents the fetus from receiving sufficient oxygen, yet the placenta receives sufficient oxygen.[143] There is a clear relationship between the amount of uteroplacental flow reduction and both the fetal and placental size.[155] In one study that looked at placentas from pregnancies with abnormal umbilical artery Dopplers, 74% of the placental weights were below the 10^{th} percentile.[156]

Histological studies of placentas from FGR infants have consistently shown features that suggest a diminished fetal perfusion of the villous vessels. In many pregnancies complicated by FGR it has been shown that they have an abnormal uterine artery Doppler, which was indicative of increased resistance in the placental vascular bed. This has been confirmed in many recent studies which have found similar results.[157–160]

This relationship has been further evaluated through Doppler ultrasounds of the umbilical vein, which have also shown a diminished perfusion in fetuses suffering from FGR.[161,162]

Placentas affected by FGR with abnormal uterine artery Doppler indices tend to demonstrate morphological abnormalities of the terminal villi. There are two hypotheses behind the reasoning for this. The first is that the abnormality is a defect in the terminal villous tree which results in reduced capillary size, and therefore, increased resistance.[163,164] The second hypothesis and the one that receives more support is that the primary event in most of these cases is a reduced uteroplacental flow leading to a placental fetal stem vasoconstriction. Secondary to those changes are changes in the terminal villous development and perfusion.[165] This hypothesis was further developed to include a reduction in placental vascularity as the cause of the increased vascular resistance.[166] This has been supported by evidence that the number of arteries in the tertiary stem villi are due to an arrest in placental angiogenesis.[143,167] These effects may be further mediated by the effects of oxygen through the VEGF directed angiogenesis.[168] Therefore, terminal villi from pregnancies complicated by fetal growth restriction and absent or reverse end-diastolic flow tend to be thinner, elongated, poorly branched, hypovascular, and have a reduction in their total volume.[169–172] However, one study found no significant correlation between uterine artery Doppler and terminal villi.[173]

Hypoxic conditions, such as decreased uteroplacental blood flow has been shown to be associated with increased apoptosis or shedding of apoptotic nuclei.[174,175] Evidence also exists to support placental apoptosis as being greater in pregnancies complicated by postplacental FGR than during normal pregnancies.[176–180] Furthermore, decreased uteroplacental blood flow has also been associated with placental infarcts,[181–183] which is in turn is associated with a reduction in fetal size.[181]

There has been considerable support from clinical experiments regarding the link between fetal and maternal circulation. A reduction in maternal blood flow to the placenta results in an increased vascular resistance within the fetal placental vasculature as well as a decreased fetal perfusion of the villi.[184] Therefore, it has been concluded that

growth restricted infants with absent or end-diastolic artery Doppler indices most likely have a high placental flow resistance due to vasoconstriction, and decreased placental weight. More detailed mechanisms can be found in a conceptual model in Appendix I.

2.3.4.2. The Role of Placental Weight and Fetal Growth Restriction

Placental weight has been shown to be directly correlated and associated with birth weight.[3–5,104] Using 317, 688 births from the Medical Birth Registry of Norway, it has been demonstrated that in pregnancies with SGA offspring, approximately 60% of pregnancies were in the lowest deciles of placental weight, but offspring that were not SGA were evenly distributed throughout the remaining placenta deciles.[185] Other studies have found similar results, indicating a significant association between birth weight and placental weight.[186–188] An association has also been found between small placental volumes in the second trimester based on ultrasound examination and the subsequent birth of an SGA infant.[4,5]

On the other hand, previous studies have also demonstrated that SGA infants have a higher proportion of placental weights at both extremes.[3–5,104,105] This is postulated to be an indication of an inefficient placenta with a reduced ability to maintain fetal growth.

Salafia et al.[130] have demonstrated that there are four additional measures other than placental weight, the most common dimension, to define placental growth including placental disk thickness, placental disk shape, placental chorionic disk diameter, and the location of the umbilical cord. These growth measures were created to capture different aspects of placental growth that are related to placental function. After categorizing disk thickness and area into three categories: $\leq 10^{th}$ percentile, $\geq 90^{th}$ percentile, and between the 10^{th} and 90^{th} percentiles for each chorionic plate area category, it was found that as the disk thickness increases, the PWR decreased.[130]

It should be noted that the placenta and fetus follow different growth patterns during gestation. The human placenta follows an S-shaped growth curve whereas fetal

growth follows an exponential pattern with most growth occurring in the third trimester. The placental reaches its peak growth between 28-30 weeks gestational and the fetal does not reach its highest growth until close to term gestation.[2] Thus, the PWR decreases during gestation.

Most studies have indicated that fetal growth is dependent on the weight of the placenta.[2–5] However, a few studies state that this implies that the placenta has no functional reserve capacity. Studies indicate that the placenta can undergo thirty to forty percent inactivation of its villous population without any effect on fetal growth or development. Consequently, the placenta has a significant functional reserve capacity.[189–192] Gruenwald suggests that since the placenta is a fetal organ it shares in growth depressions. Therefore, the small fetus not only has a small liver and heart, but also a small placenta. Thus, the placenta is small because the fetus is small, and not vice versa.[193] This was supported by Lang et al.[155] when he showed that a restriction in uteroplacental blood flow resulted in a significant decrease in placental weight, as well as reductions in the fetal heart, liver, lungs and thymus weight,[155] significant of postplacental hypoxia. Consequently, Gruenwald[193] concludes that the placenta mass cannot directly limit the fetus weight, but rather the placenta is small because the fetus is small.

2.3.4.3. Placental Function and Placental Weight

Reduction in placental size in pregnancies complicated by FGR is postulated to operate through a reduction in uteroplacental blood flow rather than as a result of an intrinsic defect in placental growth.[135] Lang et al. [155] have found that moderately restricted uteroplacental blood flow results in a lower placental weight (302±24) than normal blood flow, and severely restricted uteroplacental blood flow in an even smaller placenta (274±61).[155]

Chronic maternal under-perfusion of the fetal villi, postplacental hypoxia, often results in a placenta that weighs less than the 10^{th} percentile based on population norms.

In this ischemic placenta, the villi become smaller and smaller as the ischemia progresses and many large syncytial trophoblastic knots form.[129,194–196] Furthermore, a decrease in placental blood flow has been shown to be associated with a decrease in placental weight.[197] Finally, animal models have shown that an increase in placental apoptosis results in a decrease in placental weight.[198,199] As previously mentioned an increase in apoptosis is characteristic of postplacental hypoxia which results in early onset FGR.

On the other hand, clinical situations such as preeclampsia that result in impaired oxygen delivery to the placenta result in excess peripheral villous capillarization. Other conditions that result in excess branching angiogenesis include pregnancy at high altitude, maternal smoking and maternal anemia. All of these categories are associated with excessive placental weight. Increased development of the peripheral villous tree may be the reason why these pregnancies are associated with normal umbilical artery Doppler. FGR presenting in late gestation is associated with accelerated maturation of the placenta.[142]

2.3.4.4. The Role of the Placental Weight Ratio, Placental Function and Placental Weight

Fetal body weight in late gestation correlates positively with placental weight during both normal pregnancy conditions and also when placental weight is reduced experimentally either by direct placental manipulations or by indirect alterations of environmental conditions during development.[132,200] When placental growth is compromised experimentally, more fetus is often produced per gram of placenta than in normal circumstances; therefore, there is a lower PWR.[201,202]

In pregnant sheep and rats, placental efficiency, which is measured using the PWR, is increased in late gestation when fetal and placental weight are reduced by maternal heat stress, glucocorticoid administration, under- and overnutrition and by restriction of placentation or uterine blood flow.[203–206] A large placenta per fetal weight appear to be less efficient regardless of whether overgrowth is produced genetically or by

environmental manipulations.[207] In recent mouse experiments, it has been proven that the lightest placenta in the litter is the most efficient, as reflected in the PWR, than the largest placenta in the litter.[208] They showed that 30% more fetus was produced by the lightest placenta than the heaviest placenta in the litter. However, longitudinal measurements of the PWR were not available in the study, but the fetal growth trajectory during the late gestation appeared to differ with regards to placental size. This study is consistent with other studies that show that fetal weight is positively correlated with birth weight at 17 days of pregnancy, but not later. They concluded that the naturally smaller placenta is able to support the growth spurt of the mouse during late gestation.[208]

SGA infants have a higher proportion of placental weights at both extremes.[3–5,104,105] This is postulated to be an indication of an inefficient placenta with a reduced ability to maintain fetal growth. Therefore, this body of literature concludes that small fetuses have small placentas. However, low PWR's are indicative of an increased efficiency of the placentas of the smaller fetuses, whereas, high PWR's are indicative of a potential failed compensation.

2.3.4.5. Animal Models relating Fetal Weight, Placental Weight and Placental Function

The sheep has been extensively studied as an experimental model for FGR with poor placental substrate supply to the fetus induced using a range of methods, including ablation of the majority of the endometrial caruncles prior to conception, induction of hyperthermia, ligation of an umbilical artery or embolization of the placenta in late gestation and maternal overnutrition in the pregnant adolescent ewe. The extent and range of fetal physiologic adaptions to chronic placental insufficiency are determined by the duration of the exposure and the degree of the severity of substrate supply restriction. A reduction in placental size or transport capacity leads to an impairment of transfer between the mother and fetus. It is well established that in sheep variations in placental weight explain up to 80% of the variation in fetal weight from early in gestation.[134,209,210]

Uterine carunclectomy results in fetuses that have a reduced placental mass resulting in chronic fetal hypoxia and hypoglycaemia across late gestations and growth restriction.[211–213] The fetus responds to the reduction in substrate availability by activation of the HPA axis and sympathetic nervous system.[214,215]

Ambient temperatures during pregnancy also influence fetal growth, specifically high ambient temperature in the first trimester of pregnancy have been shown to be associated with lower birth weight.[216] There is a reduction in both absolute uterine and umbilical blood flow in the hyperthermic fetus.[217] Both placental and fetal weight are reduced by approximately 50% in growth restricted fetuses of hyperthermic ewes at 135 days of gestation, and the PWR is significantly increased.[218] The reduction in placental weight is not due to a decrease in the number of the placentomes, but instead due to a reduction in the size of the placentomes.[218] Key changes occur in placental vascular growth factors and their receptors and may reflect a compensatory response that contributes to the decrease in placentome size. These smaller placentomes have a reduced capacity for oxygen and nutrient transport to the fetus.[218]

Single umbilical artery ligation causes reduced placental blood flow and, therefore, a reduction in substrate transfer from the ewe to the fetus. Relative to fetal weight, there is a decrease in umbilical blood flow with increasing gestational age.[219] This results in chronic hypoxia and a growth restricted fetus. Single umbilical artery ligation fetuses are about 22% smaller than control fetuses.[220] The fetal adaptations to this insult included early activation of the HPA axis.[221] Placental embolization results in acute decreases in placental substrate supply leading to fetal hypoxia and growth restriction.[222,223]

Increased nutrient intake during pregnancy in adolescent ewes results in increased maternal weight gain, but decreased placental growth and a growth restricted fetus.[224] Increased food intake results in reduced uterine and umbilical blood flow.[225] Both placental and fetal weights are decreased from as early as 95 days of gestation. The decrease in placental weight is due both to a decrease in the number and the weight of the

placentosomes.[226] In addition, the fetus is hypoxic and exhibits brain sparing.[225] There is a decrease in umbilical uptake of both oxygen and glucose in the FGR fetuses of high compared with moderate nutrient intake adolescent ewe fetuses.[226] However, there is no difference in the glucose transfer capacity on a placental weight basis between the two groups.[225] In addition, there is no difference in placentome GLUT-1 or GLUT-3 mRNA expression in FGR fetuses at 81 or 133 days gestation.[226] This finding is important because it suggests that the FGR fetus is the result of a small placenta rather than altered placental function. Adolescent overfeeding leads to decreased placental size, not placental function, which results in reduced fetal substrate supply and FGR. In response to the reduced substrate supply, the fetus does not activate the HPA axis, contrary to observations in the other four sheep models of FGR, possibly due to a more moderate degree of chronic fetal hypoxia.[226]

2.3.5. Risk Factors for Abnormal Placental Weights

A variety of risk factors for extreme placental weights have been identified in the literature. Many maternal anthropometric measurements have been found to be positively associated with placental weight including: maternal height,[227] early or pre-pregnancy maternal weight,[5,227,228] early or pre-pregnancy body mass index (BMI),[229,230] and maternal weight gain.[227,228,230] A number of medical conditions have also been shown to be associated with placental weight, and they include: diabetes mellitus which results in a larger placenta,[231–233]and hypertension[234] and decompensated cardiac disease[235] which are both associated with lower placental weights.

Parity is positively associated with placental weight,[227,228,3] as is maternal life stress.[236] Results are divided on the proposed association between maternal age and placental weight,[228,237] and infant sex and placental weight.[2,3,230] However, placental weight is higher in African Americans[228] and lower in those of Asian ethnicity[238] when compared to all other ethnic groups.

Some placental factors, such as placenta abruption, placental previa and antepartum hemorrhage are not individually associated with placental weight,[229] but as a group are associated with a decreased PWR.[188] Also, both abnormal cord insertion, marginal and velamentous, and cord length below 25cm are associated with a decreased placental weight.[2,229] In addition, a single umbilical artery is also associated with a reduced placental weight.[229] Furthermore, abnormal cord insertion has also been found to be associated with a high PWR.[239] However, other factors were not controlled for in the aforementioned study. Eccentricity of cord insertion is associated with a sparser chorionic vascular distribution, and, ultimately, with a reduced transport efficiency of the placental vasculature. The latter results in a reduced birth weight for a given placental weight. Velamentous and even marginal cord insertion has been moderately associated with small placentas and small fetuses. [239]

Some of the more complex associations and their mechanisms are described below including the roles of pregnancy nutrition, gestational diabetes, psychosocial stress, smoking, preeclampsia and anaemia on placental weight. Two conceptual models indicating the risk factors for SGA and LGA infants, an increased or decreased placental weight, and those covariates which are risk factors for both fetal and placental growth can be found in appendix C and D. Also, a table showing which risk factors increase or decrease the placental weight and are associated with either SGA or LGA can be found in appendix F. Finally, a conceptual model showing proposed pathways for an abnormal PWR can be found in appendix E.

2.3.6. Mechanisms for Risk Factors of Abnormal Placental Weights

2.3.6.1. Pregnancy Nutrition

Placental weight correlates with nutrition during pregnancy, but the effects of maternal under-nutrition depend on the timing and duration of the nutritional deprivation. A highly cited example that outlines this is the Dutch Famine of 1944-1945 in which women who were subjected to starvation during their third trimester had low placental

weight. However, the PWR's were unaltered when compared to women who were not malnourished.[124]

Animal models of maternal nutritional deprivation confirm that nutritional deprivation is able to limit placental growth, thereby limiting fetal growth. However, it has been found that placental total glucose transport capacity was normal when expressed based on a unit weight-specific placental basis. Therefore, the investigators concluded that the major limitation to fetal growth is the small size of the placenta rather than alterations in its nutrient metabolism or transfer capacity.[6]

Both under- and over-nutrition during pregnancy affect placental size, although the specific effects depend on the severity, duration and gestational age at the onset of nutritional change.[124,240] In sheep, moderate undernutrition during the peri-conceptual period alone has no effect on placental weight in late gestation,[241,242] but when the period of undernutrition is during the period of rapid placental growth, placental weight is frequently increased near term.[243–245] This overgrowth appears to act as a compensatory mechanism for the reduced nutrient availability early in gestation as fetal weight is normal, or even enhanced, in late gestation after normal nutrition has been restored.[246] Similar compensatory increases in placental weight have been observed in response to undernutrition in pregnant pigs, rats and humans.[124,247] By contrast, moderate undernutrition during mid to late gestation when the placenta has formed tends to reduce placental weight near term.[243–245] When nutrient deprivation occurs throughout pregnancy in sheep and rats, fetal and placental weights both decrease, but usually more fetus is produced per gram of placenta than in normally nourished animals; therefore, the PWR is lower.[240,247,248] Similar increases in placental efficiency are observed when placental and fetal growths are retarded by glucocorticoid administration during late gestation.[205,249] Exposure to poor nutrition or glucocorticoids at critical stages of placental development, therefore, appears to increase the efficiency with which the small placenta transfers nutrients to the fetus.[250] Therefore, placental weight may be increased or decreased depending on the timing or duration of the maternal under or over nutrition based on a combination of epidemiological and animal studies.

2.3.6.2. Gestational Diabetes

It has been noted by several authors that the placentas from women with gestational diabetes are often increased in weight when compared to women who had only one abnormal oral glucose tolerance test.[234,251–255]

A high PWR has also been found in women with gestational diabetes, which the authors indicated is from an increased placental weight rather than a decreased birth weight.[252] However, another study has found a significantly lower PWR for women with gestational diabetes compared to women with no glucose intolerance.[256] Nevertheless, a significantly higher placental weight was found in this study, so the decreased ratio is the result of lower birth weights. These findings were based on a placental weight of one standard deviation away from the established value for appropriate-for-gestational age infants from non-diabetic pregnancies.

There is a modification in placental glucose transporters, yet there is an unchanged transplacental glucose transport in gestational diabetes.[257] Amino acid transport may also be altered in diabetes.[258] Furthermore, the placental structure is altered in diabetes. The surface and exchange areas are enlarged as a result of the hypoproliferation and hypervascularization. Therefore, the maternal-placental oxygen supply is reduced, and the fetal oxygen demand is increased.[259,260] This phenomenon could be explained by aerobic metabolism which is stimulated by fetal hypersinsulinemia. The low oxygen level upregulates transcriptional synthesis of leptin, vascular endothelial growth factor (VEGF) and fibroblast growth factor which promotes placental endothelial cell proliferation. The result is enhanced vascularisation of the placenta.[261,262] The hyperglycemia can induce a reduction in trophoblast proliferation which delays placental growth and development, especially in early gestation. It has also been shown that matrix metalloproteinases (MMP), MMP14 and MMP15, are increased in diabetes and are associated with invasion, angiogenesis and proliferation.[263]

2.3.6.3. Smoking

Cigarette smoking is associated with a decreased fetal weight, but of the few studies that have looked at maternal smoking and placental weight, there has been no significant effect found.[228,264–268] However, some studies that investigated the PWR found a significant difference between the ratios in smokers versus non-smokers. The PWR were significantly higher in smokers than in non-smokers in two prospective cohort studies.[227,266] On the other hand, another study found a significantly lower PWR for smokers than non-smokers.[264] Therefore, the results are divided on the effect of smoking on the PWR, but the above studies lack a large sample size and are dated.

When a mother smokes during pregnancy the placenta and fetus become hypoxic because of reduced oxygen content within maternal blood, referred to as preplacental hypoxia. This condition results in reduced intraplacental oxygen content, predominately branching angiogenesis, and reduced vascular impedance. The increase in branching angiogenesis and thereby reduced vascular impedance, is an adaptive mechanism to the hypoxic state. Interestingly this mechanism is associated with excessive placental weight.[144]

2.3.6.4. Preeclampsia

Placentas from women with preeclampsia tend, on average, to be smaller than those from pregnancies that are uncomplicated.[105,185,228,269] However, the decrease is only slight and the relationship between the two is weak. Also, the PWR is often increased in pregnancies that are complicated with preeclampsia,[231,270] which suggests that there is compensatory growth of placental villi in an attempt to overcome an unfavourable maternal environment.[208,271] However, the duration of the disease, and the severity of preeclampsia are important determinants of placental abnormality. In a large population study, it was found that low placental weight was strongly associated with preterm preeclampsia, but less strongly associated with term preeclampsia. Surprisingly, term preeclampsia was associated with both low and high placental weights.[272]

According to current knowledge, preeclampsia is initiated by a hypoxic placenta which is the consequence of reduced trophoblast invasion and impaired transformation of the decidual spiral arteries. Alterations in trophoblast differentiation occur in many pathophysiological conditions of pregnancy including both FGR and preeclampsia. The mechanism behind this is postulated to be associated with a defect in EVT invasion. Some of the spiral arteries are not invaded and some are superficially invaded, which leads to a reduced blood flow in the intervillous space and a hypoxic placenta.[273]

EVT apoptosis is seen in normal pregnancy, but in preeclamptic pregnancies 15 to 50 percent of cells are apoptotic, which is a finding associated with macrophages around the spiral arteries.[273] Furthermore, during normal pregnancy, syncytiotrophoblast fragments are dispersed into the mother's circulation as a result of apoptosis. However, the rate of syncytiotrophoblast apoptosis is increased from 2 to 3 percent in a pregnancy not complicated by preeclampsia and from 5 to 6 percent in pregnancies complicated by preeclampsia.[274]

The mechanism behind term preeclampsia's effect on FGR is that normally oxygenated maternal blood has restricted entry into the uteroplacental tissues due to either occlusion or failed trophoblast invasion of the uteroplacental arterioles. This situation represents late onset IUGR with preserved end diastolic flow volume. This condition results in reduced intraplacental oxygen content with increased predominately branching angiogenesis and reduced vascular impedance as an adaptation to the reduced oxygen entering the placenta.[142]

2.3.6.5. Anaemia

Many researchers have noted that placentas tend to be heavy in pregnancies complicated by both severe and mild maternal anaemia, with the fetus often being small, and therefore the PWR increased.[228,275–277] The increased placental weight, and therefore ratio indicate that anaemia, rather than underlying iron deficiency, is the cause for an

increased placental ratio.[278–280]However, many of these studies suffer from the methodological issue of too few placentas being examined. In contrast, in two large studies the weight of the placenta was found to be inversely proportional with the maternal haemoglobin concentration.[281,282]

The increased size of the placenta has been understood as a compensatory mechanism to overcome the lack of oxygen in the maternal blood, again referred to as preplacental hypoxia, as well as the increased trophoblastic proliferation and placental angiogenesis that result from anaemia.[283] In response to a lack of oxygen, the extravillous trophoblast of the placenta bed shows an increased depth of invasion.[284]

2.3.7. Outcomes Associated with Abnormal Placental Weight Ratios

Both an abnormally low and abnormally high PWR are associated with adverse outcomes. A PWR below the 10th percentile has been found to be significantly associated with fetal distress.[285] Alternatively, placental weight above the 90th percentile was found to be significantly associated with newborns requiring neonatal intensive care admission.[104]

There are numerous adverse short term outcomes associated with abnormal PWR's. Infants with a high PWR had increased incidence of meconium stained liquor, hypocalcaemia, hypomagnesaemia and phototherapy. The incidence of these outcomes was maintained even after exclusion of the preterm infants.[286] The neonates with a high PWR had increased incidence of low 1-minute Apgar score, treatment for neonatal jaundice and infection, and respiratory complications. After adjusting for the effects of preterm birth and vaginal delivery, a high ratio was still associated with low Apgar score, respiratory complications, and treatment for infection.[287]

There are several long term outcomes associated with both abnormal PWR's and abnormal placental sizes. Placental insufficiency, as defined by reduced uterine perfusion, in the pregnant rat results in low birth weight offspring predisposed them to

the development of hypertension.[288] Barker and his colleagues noted in 1990 that an increased placental weight was associated with an increased risk of hypertension in adults between 46 and 54 years of age.[289] In addition, a large prospective cohort found that after 45 years of follow-up, the sex- and cohort-adjusted hazard ratio for the highest versus the lowest third of the PWR was 1.38. Therefore, the authors concluded that a high PWR was associated with increased risk of cardiovascular disease and death from cardiovascular disease.[137]Also, a reduced placental weight and surface area is associated with hypertension in later life, and the effect was strongest among women who were short and had a low socioeconomic status. In the offspring of tall, middle class mothers, who were likely to have been the best nourished, hypertension was predicted by large PWR. The odds ratio rose from 1.0 if the PWR was 0.17 or less to 1.9 if the ratio was more than 0.21. The authors suggested that the risk of developing hypertension relative to your PWR was dependant on the maternal nutritional state.[290] Two studies have found that in 8 and 9 year old children an increased placental weight at birth is associated with increased systolic blood pressure.[291,292]

2.4. Summary and Rationale for this Study

SGA infants are an important population to examine because mortality and morbidity are increased in SGA infants compared to those who are AGA.[92] Short term complications include still birth, abnormal EFH, hypoglycemia, hypocalcemia, polycythemia, depression, meconium, 1 minute apgar less than 6, 5 minute apgar less than 6, 1 minute apgar less than 3, and in hospital death, all of which increase with increasing severity of growth restriction.[106,293–295]

A decreased birth weight shares many of the same risk factors as a decreased placental weight. However, some risk factors have differing effects on both placental weight and birth weight, but the literature has yet to elucidate these differences. Therefore, by determining the risk factors associated with an abnormal PWR, it will provide a clearer understanding of the variables that are associated with the relationship between fetal and placental growth.

Birth weight is correlated with placental weight, yet SGA infants often have high PWR ratios indicative of more grams of placenta per gram of birth weight. This is postulated to occur as the result of a compensatory mechanism in response to a decrease in nutrient or oxygen delivery through the placenta to the fetus. Nevertheless, the timing and duration of the reduced nutrient or oxygen supply plays an integral role in both fetal and placental growth.

PWR distributions will make a substantial contribution to the literature. While it is suspected that PWR may be an important indicator of fetal health, there are few population standards for comparison. There are only one other set of PWR percentile curves in a Canadian population, and their sample sizes are much smaller than our sample. Therefore, our percentiles provide more accurate predictions, especially at the extremes[296] Determining the differences in PWR's between SGA, AGA and LGA infants will provide a better understanding of the relationship between fetal growth and placental growth. To date, they will be the first of their kind in the literature. Also, the placenta and birth weights follow different patterns of growth during gestation. The creation of distributions based on gestational age will provide a better understanding of the differences in the ratio of these two measures across gestational age. They will be a useful tool to provide standards in the literature for other researcher and clinicians to use. Therefore, by creating gender specific PWR distributions by gestational age, it will provide deeper insight into critical periods for both fetal and placental growth.

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CHAPTER 3: METHODS

3.0 Introduction

This chapter describes the generic methods for the entire thesis including descriptions of covariates and outcomes variables and their recoding for analyses, as well as details on the specific methods used for each objective. More specifics will be provided in the subsequent manuscript chapters.

3.1 Design and Data Source

This was a retrospective cohort study, using a hospital database of all singleton birth records from St. Joseph's Health Care and Victoria Hospital in London, Ontario. The administrative perinatal database housed at Victoria Hospital contained information on 58,004 births for the study date range. The perinatal database contains information on maternal demographics, perinatal risk factors, and maternal and fetal outcomes.

Guided by definitions in the Vital Statistics Act, the database prospectively collected data on all infants whose birth weight was greater than or equal to 500g or whose gestational age was greater than 20 weeks. Relevant data abstraction from the medical records was performed and input into the database.

3.2 The Study Population

3.2.1 Inclusion and Exclusion Criteria

The first objective included all singleton births from St. Joseph's Health Care and Victoria Hospital in London, Ontario between April 1, 2001 and March 31, 2011. The second objective included all singleton births from both hospitals between June 1, 2006 and March 31, 2011 due to the availability of covariates of interest in the database. The mothers were from London, Ontario and the surrounding area of Southwestern Ontario. St. Joseph's Health Care and the London Health Sciences center are tertiary care centers, and therefore data represent mainly urban residents, as well as high risk transfers from rural areas that amount to approximately 20% of births at the hospitals. Mothers were

predominately from Middlesex County; however, there were mothers from the surrounding area.

Women who delivered an infant before 22 or after 42 weeks were excluded due to the small sample sizes present in these categories. Also, unknown or ambiguous genders were excluded from the analysis, as the distribution curves were stratified into males and females. Infants with major congenital abnormalities and stillbirths were also excluded. Lastly, multiple pregnancies were excluded from the analyses. These exclusions are highlighted separately for each objective in the study flow charts in Figures 3.1 and 3.2.

3.2.2 Missing Information

For both the first and second objective, any observation with a missing placental weight ratio (PWR) or gestational age was excluded from the analyses. For objective two, there was missing information for smoking status, preeclampsia, anaemia, placenta delivery method, parity, maternal age, and maternal height. Any individual with missing information was excluded for this objective.

3.3 Data Collection and Coding

3.3.1 Predictor Variables

The following variables were chosen to be extracted from the perinatal database, according to the conceptual model, to be considered as predictors of the placental weight and/or birth weight. The categorization process is described below for each of the predictor variables, where these variables and their coding are summarized in Table 3.1.

3.3.1.1 Baseline Variables

3.3.1.1.1 Maternal Height

Maternal height was treated as a continuous variable because categorizing continuous variables is a subjective process that leads to variables with less statistical information.[1] All measurements were converted to metric units for analysis.

3.3.1.1.2 Parity

The number of live births to this mother (counting twins and triplets as 2 and 3 births, respectively) was used for the parity count. For this study, parity was dichotomized for the analysis into nulliparous versus multiparous with women completing their first pregnancies as the reference group.

3.3.1.1.3 Smoking Status

Smoking status was entered as a binary variable, whether the person smoked during the pregnancy or whether they did not. This variable did not account for the number of cigarettes smoked. The women who did not smoke were treated as the reference group.

3.3.1.1.4 Maternal Pre-Pregnancy Weight

The perinatal database considered it acceptable to use weight at presentation, if gestational age was 16 weeks or less at presentation. The pre-pregnancy or early pregnancy weight from the antenatal record was entered if gestational age was 16 weeks or younger, but preferably pre-pregnancy weight was used. The data holds greater validity if it can be cross-referenced against other documentation in the chart. The pre-pregnancy or early pregnancy weight from the antenatal record was not entered unless it could be cross-referenced against the Nursing Admission sheet and/or the first Obstetrician consult note on Power Chart and/or the Obstetrician or general practitioner appointment on the second page of the antenatal history and/or the history taken by the clerk on admission. The Nursing Admission sheet shows the weight at admission and the self-reported weight gain during the pregnancy. If this corroborated with the other weight information the abstractor noted in the chart, then it was entered as pre-pregnancy or early pregnancy weight. It was also entered if in the chart it was specifically documented as pre-pregnancy weight. If the weight in the antenatal record was taken at gestations greater than 16 weeks it was not used and the field was left blank. Therefore, maternal pre-pregnancy weight was treated as a continuous variable, and all measurements were converted to metric units for analysis.

3.3.1.1.5 Maternal Age

When the mother's age at time of delivery was entered into the database it was calculated by subtracting the mother's date of birth from the infant's date of birth. Age remained was categorized into mothers <21 years of age, between 22 and 34 years of age and <34 years of age for the analyses.

3.3.1.1.6 Maternal BMI

Maternal BMI was not directly collected in the database, but the maternal weight and height variable were used to calculate maternal pre-pregnancy body mass index (BMI) using the equation BMI= weight (kg) / height^2 (m^2). BMI was then categorized according to the Health Canada Guidelines into four categories: underweight (< 18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obese (30.0+).[2] Those observations with a normal BMI were used for the reference category.

3.3.1.1.7 Maternal Asthma Status

Maternal asthma status was coded as a binary variable. The mother was either asthmatic or not asthmatic based on information in the patients chart. The mothers who did not have asthma were the reference group.

3.3.1.2 Mid-Pregnancy Variables

3.3.1.2.1 Gestational Hypertension

Gestational hypertension was defined as diastolic blood pressure > 90 mm Hg, on at least two occasions at 20 weeks gestation or older, no proteinuria and blood pressure elevation detected for the first time during pregnancy. It was coded as gestational hypertension even if the physician only noted "elevated blood pressure" in their notes, as directed by the Chief of Obstetrics, Dr. Natale. If the diagnosis on the chart was unclear then the mentioned guidelines were used to define gestational hypertension.

An expansion of the definitions was provided in April 2010, as help for coding a chart with inconsistent documentation. For example, if the physician noted that the

patient had gestational hypertension but lab results showed proteinuria, then the database coded preeclampsia, as per Dr. Natale.

3.3.1.2.2 Preeclampsia

Severity of hypertensive disorder was recorded as a categorical variable. The patient either had no hypertension and proteinuria or gestational hypertension with a diastolic pressure >90 mm Hg, on a least two occasions at 20 weeks gestation or lower, no proteinuria, and blood pressure elevation detected for the first time during pregnancy. The patient could also have been categorized as having mild preeclampsia defined as diastolic blood pressure between 90 and 110mm Hg with proteinuria less than 3+ or severe preeclampsia defined as diastolic pressure of 110 mm Hg or higher and/or 3+ protein and/or any end-organ involvement and treatment with magnesium sulfate or eclampsia when seizures occur or unknown. In cases where a physician noted that a patient had gestational hypertension but, lab results showed proteinuria, then the data abstractor recorded preeclampsia. These guidelines were used when the diagnosis on the chart was unclear. If any proteinuria was present it was coded as preeclampsia up to and including the third day postpartum based on the diagnostic criteria from the SOGC recommendation IIIC from March 2008. Codes followed classification in Creasy-Resnick, maternal-fetal medicine, 6th edition.[3] For any case with preeclampsia superimposed on chronic hypertension, chronic hypertension was defined based on the criteria provided in the hypertension section, and then the appropriate code for preeclampsia severity was also entered. For this thesis the data were coded as a binary variable, preeclampsia or no preeclampsia present. The group with no preeclampsia was treated as the reference group.

3.3.1.2.3 Gestational Diabetes

Carbohydrate disorders were defined using a categorical variable in the perinatal database. Mothers were defined according to the following set of criteria: no carbohydrate disorder, carbohydrate intolerance defined as one abnormal reading on a 75 gram oral glucose tolerance test, gestational onset and diet controlled, gestational onset with insulin control or overt diabetes. When cases of gestational onset diabetes were

commented on by the doctor as “missed”, it was coded as gestational onset with insulin control unless a specific diagnosis of overt diabetes was indicated. In this study, gestational diabetes was coded as a binary variable, present or absent. Mothers' with no gestational diabetes were used for the reference group.

3.3.1.3 Umbilical and Placental Conditions

3.3.1.3.1 Umbilical Cord Risk Factors

In the database, cord complications were defined categorically depending on the presence or absence of a cord complication and the type of complication. For the analysis in this study, no complications acted as the reference group. An infant was placed into one of the following three categories: no complications, a cord around the neck, in a knot, around the body, prolapsed or lacerated or having a short, 2-vessel or velamentous umbilical cord.

3.3.1.3.2 Placental Abruption

Placental abruption was defined in the database as premature separation of a normally implanted placenta after the 20th week of gestation and before the fetus was delivered. Placental abruption was categorized as either none, mild, moderate or severe in the perinatal database. If the placental abruption was recorded as chronic on the mother’s chart, then it was coded as a mild abruption. This addition to the coding manual for chronic abruption was added in May/June of 2010. For the purpose of this thesis, the data were coded as a binary variable, either abruption (mild, moderate or severe) or no abruption. The observations with no placental abruption were used as the reference.

3.3.1.3.3 Placental Previa

Placental previa was categorized into five different categories. Placental previa is either indicated as not present, marginal, partial, complete or resolved before delivery. The database defines placental previa as implantation of the placenta low in the uterus either overlying or reaching the vicinity of cervical opening. Prior to May/June of 2010 the final category listed above, resolved before delivery, was not one of the categories for

placental previa. For this thesis, placental previa were treated as a binary variable, and women with no placental previa were treated as the reference group.

3.3.1.4 Late Pregnancy and Delivery Variables

3.3.1.4.1 Pregnancy Weight Gain

Weight gain during pregnancy was only documented as a risk factor in the perinatal database, and not as an exact weight value. Therefore, a mother was defined as having a low pregnancy weight gain if by 30 weeks gestation the mother has gained <10 pounds or if at delivery the mother has gained <20 pounds. Furthermore, the pregnancy weight gain was indicated as high if the mother gained >40 pounds during her current pregnancy at the time of delivery. Women who gained within the normal range for weight gain during pregnancy were not indicated, so women who were not categorized as having a low or high weight gain were presumed to be within normal ranges. Also, the exact weight gain was not indicated, but instead recorded as a categorical variable. The women with normal weight gain were used as the reference group.

3.3.1.4.2 Anemia

In the perinatal database admission hemoglobin was recorded. If admission hemoglobin was <100g/L then the patient is defined as anemic. This variable was coded as a binary variable, present or absent. Patients with admission hemoglobin within normal limits were treated as the reference category.

3.3.1.4.3 Sex of the Infant

Sex was defined as either: ambiguous, male, female or unknown if the data was missing. Therefore, the sex of the infant was categorized as a binary variable, either male or female, for all statistical analysis. Unknown or ambiguous genders were excluded from the analysis, as previously mentioned.

3.3.1.4.4 Placental Delivery

The database coding manual indicates that a good indication of problems with delivery is the interval of time from the infant date of birth to the delivery of placenta,

usually 30 minutes or more of placental retention. The placental delivery was categorized into spontaneous, expressed or assisted, manual, if 30 minutes or more after vaginal delivery of baby and always manual if the delivery was a cesarean section, retained, if dilation and curettage, or by scraping or curettage, and finally unknown. This variable remained as a categorical variable based on the aforementioned categories, and a observations with a spontaneous placenta delivery were used as the reference.

3.3.1.4.5 Congenital Abnormality

Congenital abnormality was recorded as a categorical variable, with the following categories: no abnormalities, minor abnormalities or major abnormalities. Any major congenital abnormalities were excluded from the analyses.

3.3.2 Outcome Variables

3.3.2.1 Gestational Age

Gestational age was a key variable for this research, as it allowed an infant to be classified as SGA, AGA or LGA and played an integral role in establishing PWR distributions by gestational age. Gestational age was recorded in the database as the number of completed weeks and the number of completed days. For the purpose of this analyses, gestational age remained as a continuous integer variable, but only the gestational week was used, not the number of days.

According to clinical practice, gestational-age estimation in the database was derived from the last menstrual period if either first trimester ultrasound was within ± 4 days of the estimated date of confinement or second trimester ultrasound was within ± 10 days of the estimated date of confinement. Otherwise, gestational age was corrected on the basis of ultrasound measurements that are routinely obtained for all pregnant women in the province of Ontario for pregnancy dating.

3.3.2.2 Birth Weight for Gestational Age

In the database, infant birth weight was recorded in grams as a continuous variable. One of the primary outcome measures of interest for this thesis was the birth

weight or size for gestational age of the infant at birth. Size for gestational age is a categorization based on the normal distribution of birth weights, controlling for infant sex and gestational age, in the population. For this study, the continuous birth weight variable was categorized into small, average and large for gestational age infants (SGA, AGA and LGA) for the analysis. This thesis used the population standards published by Kramer et al. in 2001.[4] A SGA infant was defined as one whose birth weight fell into the lowest 10% of Canadian births, for their sex and gestational age. LGA infants were defined as those whose birth weight fell into the highest 10% of Canadian births, for their sex and gestational age. Infants who did not fall into either the lowest or the highest 10% of birth weights were considered to be AGA. AGA infants were used as the reference category for this analysis.

3.3.2.3 Placental Weight

Another primary outcome measure of interest for this thesis was placental weight. Placental weight was entered into the database in grams, and if unknown was left blank. This variable has been collected since the beginning of the database at St. Joseph's Hospital, but only since November of 2003 in the LHSC, Victoria Hospital database. For objective one of this thesis, placental weight was treated as a continuous variable in order to produce accurate distributions. For objective two of this thesis, it was categorized into $\leq 10^{th}$ percentile, $\geq 90^{th}$ percentile or in between the 10^{th} and the 90^{th} percentile based on the results from objective one, using the overall standards that were created.

3.3.2.4 Placental Weight Ratio

The PWR was calculated by dividing the birth weight by the placental weight for each infant that has a birth weight and a placental weight.

3.4 Data Analysis

3.4.1 Data Cleaning

Exploratory univariate analyses detected implausible values, missing values or other questionable or extreme values that required attention. Additional work was done to clean and quantify the predictor and outcome variables to ensure that implausible values were not included. Variables such as maternal height, age and pre-pregnancy weight were trimmed at the 1st and 99th percentile in order to remove implausible values. Birth weights greater than three standard deviations from the mean were removed, as they were presumed to be implausible. The calculation for this can be found in Appendix J. Placental weights < 100g or >2500g were also removed, as they were presumed to be incorrect. Due to the large size of the population, the implausible or extreme values could not be cross checked with the chart information. A diagrammatic representation of this can be found in the study flow chart in Figures 3.1 and 3.2.

3.4.2 Statistical Analyses

3.4.2.1 Placental Weight Ratio Distributions

3.4.2.1.1 Justification and Explanation: Quantile Regression

Quantile regression (QR), which was introduced by Koenker and Bassett is way to create growth charts.[5] One of the main advantages of QR is that it does not make any distributional assumption beforehand. It is able to model data with heterogeneous conditional distributions.[6] It is also relatively easy to accommodate other covariates besides age; however, this function will not be required for the specific aims of this thesis. Computationally, QR is fast and stable. It also generalizes the concept of a univariate quantile to a conditional quantile given one or more covariates.[7] Another advantage of QR, is that it is robust to extremes of the response variable.[6]

Ordinary least-squares regression models the relationship between one or more covariates X and the conditional mean of a response variable Y given X = x. In contrast, QR models the relationship between X and the conditional quantiles of Y given X = x, so it is especially useful in applications where extremes are important, such as growth studies where upper and lower quantiles are critical from a diagnostic perspective.[8] QR also provides a more complete picture of the conditional distribution of Y given X = x when both lower and upper, or all quantiles, are of interest. The main advantage of QR

over least squares regression is its flexibility for modeling data with heterogeneous conditional distributions, such as the PWR ratio.[8] QR provides a complete picture of the covariate effect when a set of percentiles is modeled, and it makes no distributional assumption about the error term in the model.

There have been several methods used to construct such age dependent growth charts. Early methods fit smoothing curves on sample quantiles of segmented age groups. However, these methods are not robust to outliers. Large sample size is needed in order to estimate the percentiles in each age group with appropriate precision. The segmentation may lose information from nearby groups. To avoid segmentation, Cole and Green[9] developed a Box-Cox transformation-based semiparametric approach from the LMS (Lamda-Mu-Sigma) method introduced by Cole. The semiparametric LMS method solves penalized likelihood equations.[10]

Generally there is reasonable agreement between LMS curves and QR. However, it has been shown that especially in infants, the more parsimonious LMS curves lack the flexibility of QR. Also, the LMS method has been shown to overfit in comparison to QR. While there is a relatively good agreement between the two methods, LMS imposes more structure but QR is more stable and is able to reveal departures from underlying assumption of parametric models.[8]

QR, which solves the optimization problem with a general simplex algorithm, is computationally expensive. Faster methods have been developed. The worst-case performance of the simplex algorithm shows an exponentially increasing number of iterations with sample size. Since the general QR fits adequately into the standard primal-dual formulations of linear programming, the interior point algorithm can be applied. The worst-case performance of the interior point algorithm has been proven to be better than that of the simplex algorithm.[6,7]

Several methods for computing confidence intervals of the regression quantiles have been proposed in the literature. They can be classified into three categories: the

direct method, which computes the confidence intervals, based on the asymptotic normality of the estimated regression quantiles; the rank-score method, which computes the confidence intervals based on the inversion of the rank-score test; and the resampling method, which uses the bootstrap technique.

3.4.2.1.2 Application: Quantile Regression

The first objective to construct PWR distribution curves by gestational age for males and females and then to stratify by SGA, AGA and LGA status was accomplished using QR. The QUANTREG procedure in SAS 9.3 computes the fitted values of the quantile only for a single quantile at a time. Therefore, since fitted values were required for multiple quantiles in this analysis, a macro was created. The macro allowed for computation of the 3^{rd}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} and 97^{th} percentiles simultaneously in one output. The FITPLOT graph option in QUANTREG was used to generate the graphs displayed in the results section which show the smoothed and fitted curves without any of the data points. The macro used is displayed in Appendix K.

QR is a type of regression analysis that aims to estimate either the conditional median or other quantiles of the response variable. QR was performed using the interior point algorithm with a tolerance of 1E-4 and a step length of 0.25. Markov chain marginal bootstraps (MCMB) were implemented to compute confidence intervals for the regression quantiles.[7,11]

The PWR was used as the outcome variable and a quadratic term for gestational age was used as the covariate. Using a quadratic term for gestational age produced the same results as when cubic B-splines were used with knots at the boundaries (22 and 42 weeks gestation). Therefore, a quadratic term was used as it allowed for an easier interpretation of the significance level of the results at each percentile.

3.4.2.2 Determinants of an Atypical Placental Weight Ratio

3.4.2.2.1 Application: Multinomial Logistic Regression

The second objective that aimed to identify risk factors for abnormal PWR's was completed in SAS 9.3 using multinomial logistic regression with the PROC LOGISTIC function. The outcome for this analysis was a PWR $\leq 10^{th}$ percentile, between the 10^{th} and the 90^{th} percentile or $\geq 90^{th}$ percentile, with a PWR between the 10^{th} and 90^{th} percentile as the reference group. The PWR standards created in objective 1 (Chapter 3) for overall infants were used to establish 10^{th} and 90^{th} percentile cut-offs for use as the outcome variable. Variables were entered in chunks,[12] and the collapsibility criteria were used to determine if any of the odds ratios (OR) changed by greater than 10% when another chunk was added. Variables were entered in chunks, in temporal sequence, into the model. These chunks were: baseline variables; early pregnancy variables; placental and cord complication variables; and late pregnancy and post partum variables. Using temporally entered chunks allowed associations between variables from different chunks to become evident through the model building process, which allowed for a better understanding of the associations in the data.[12] Multinomial logistic regression allowed us to use infants with a PWR between the 10^{th} and 90^{th} percentile as the reference group in an analysis that simultaneously estimated the odds of a PWR$\leq 10^{th}$ percentile or $\geq 90^{th}$ percentile. Entering chunks allowed associations between variables from different chunks to become evident through the model building process, which allowed for a better understanding of the associations in the data.

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Table 3.1: Study Variables and Recoding for Analysis

Variables Available in Database	Coding in the Database	Recoding for Analysis
Birth Date	Recorded as a year and a month	
Birth Weight	Measured in grams	***Categorical*** 0=SGA 1=AGA 2=LGA
Gestational Week	Measured in weeks	***Continuous (Integer)***
Placental Weight	Measured in grams	***Continuous***
Maternal Age	Measured in years	***Categorical*** <21 years of age 21-34 years of age >34 years of age
Maternal Height	Measured in inches	***Continuous***
BMI	Not recorded by pre-pregnancy weight and maternal height were used to create this variable	***Categorical*** 0=BMI <18.5 1=18.5≤BMI<24.9 2=24.9≤BMI<29.9 3=BMI≥29.9
Parity	Recorded as a continuous variable	***Binary*** 0=primiparous 1=multiparous
Admission Hemoglobin	Measured in grams per Liter.	***Binary*** 0=not anaemic (If admission hemoglobin in ≥100g/L) 1=anaemic (If admission hemoglobin is <100g/L)
Sex	A=Ambiguous F=Female M=Male U=Unknown (missing information)	***Binary*** 0=Male 1=Female
Gestational Diabetes	0=No 1=Carbohydrate intolerance (1 abnormal reading on a 75 gram oral glucose tolerance test (GTT) 2=Gestational onset, diet controlled	***Binary*** 0=No (If previously coded as 0 , 1 or 4 in the database) 1=Yes (If previously coded as 2 or 3 in the database)

	3=Gestational onset, insulin controlled 4=Overt. Note: cases of gestational onset with comment of "missed" by Dr. should be coded as 3 unless a specific diagnosis of overt diabetes has been made.	
Preeclampsia	0=No 1=Gestational hypertension, diastolic > 90 mm Hg, on at least 2 occasions at 20 weeks gestation or older, no proteinuria, blood pressure elevation detected for the first time during pregnancy. Code as gestational hypertension even if physician only notes "elevated blood pressure", as directed by Dr. Natale. 2=Mild preeclampsia, diastolic between 90 and 110 mm Hg with proteinuria less than 3+ 3=Severe preeclampsia, diastolic 110 or higher, *and/or* 3+ protein, *and/or* any end-organ involvement and treatment with magnesium sulfate 4=Eclampsia, seizures occurs -8=unknown	***Binary*** 0=No (If previously coded as 0 or 1 in the database) 1=Yes (If previously coded as 2, 3 or 4 in the database)
Smoking Status	0=No (during pregnancy) 1=Yes (during pregnancy)	***Binary*** 0=No 1=Yes
Umbilical Cord Complications	0=None 1=Neck 2=Knot 3 =Body 4=Prolapsed 5=Laceration 6=Short 7=2-vessel 8=Velamentous 9=Other	***Categorical*** 0=None 1=Neck, body, prolapsed, lacerated, and other 2=short, 2-vessel and velamentous

Placental Abruption	0=No 1=Mild (may be recorded on chart as "chronic") 2=Moderate 3=Severe	***Binary*** 0=No (If coded in database as 0) 1=Yes (If coded in database as 1, 2 or 3)
Placental Previa	0=No 1=Marginal 2=Partial 3=Complete 4=Resolved before delivery	***Binary*** 0=No (If coded in database as 0) 1=Yes (If coded in database as 1, 2, 3 or 4)
Placenta Delivery	1=Spontaneous 2=Expressed or assisted 3=Manual, if 30 minutes or more after vaginal delivery and always manual if C/S delivery 4=Retained, if D&C *or by scraping or curettage only* -8 =unknown	***Categorical*** 1=Spontaneous 2=Expressed or assisted 3=Manual, if 30 minutes or more after vaginal delivery and always manual if C/S delivery 4=Retained, if D&C *or by scraping or curettage only*

Figure 3.1: Flow chart illustrating the process by which the study population was obtained for Objective 1

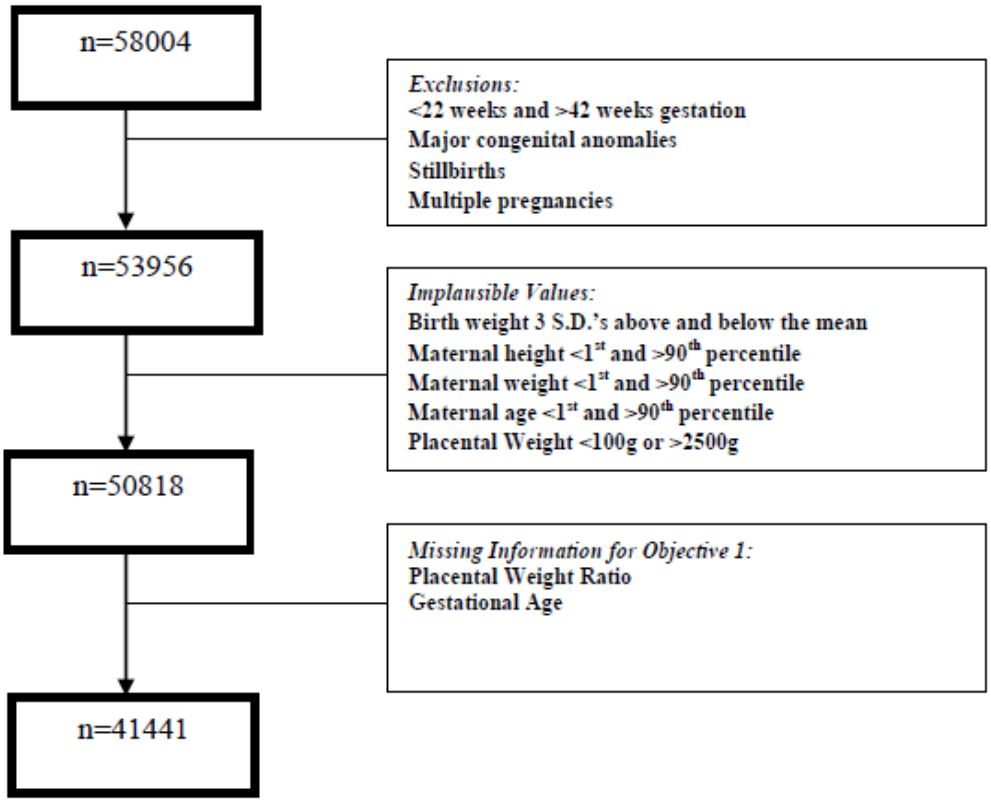
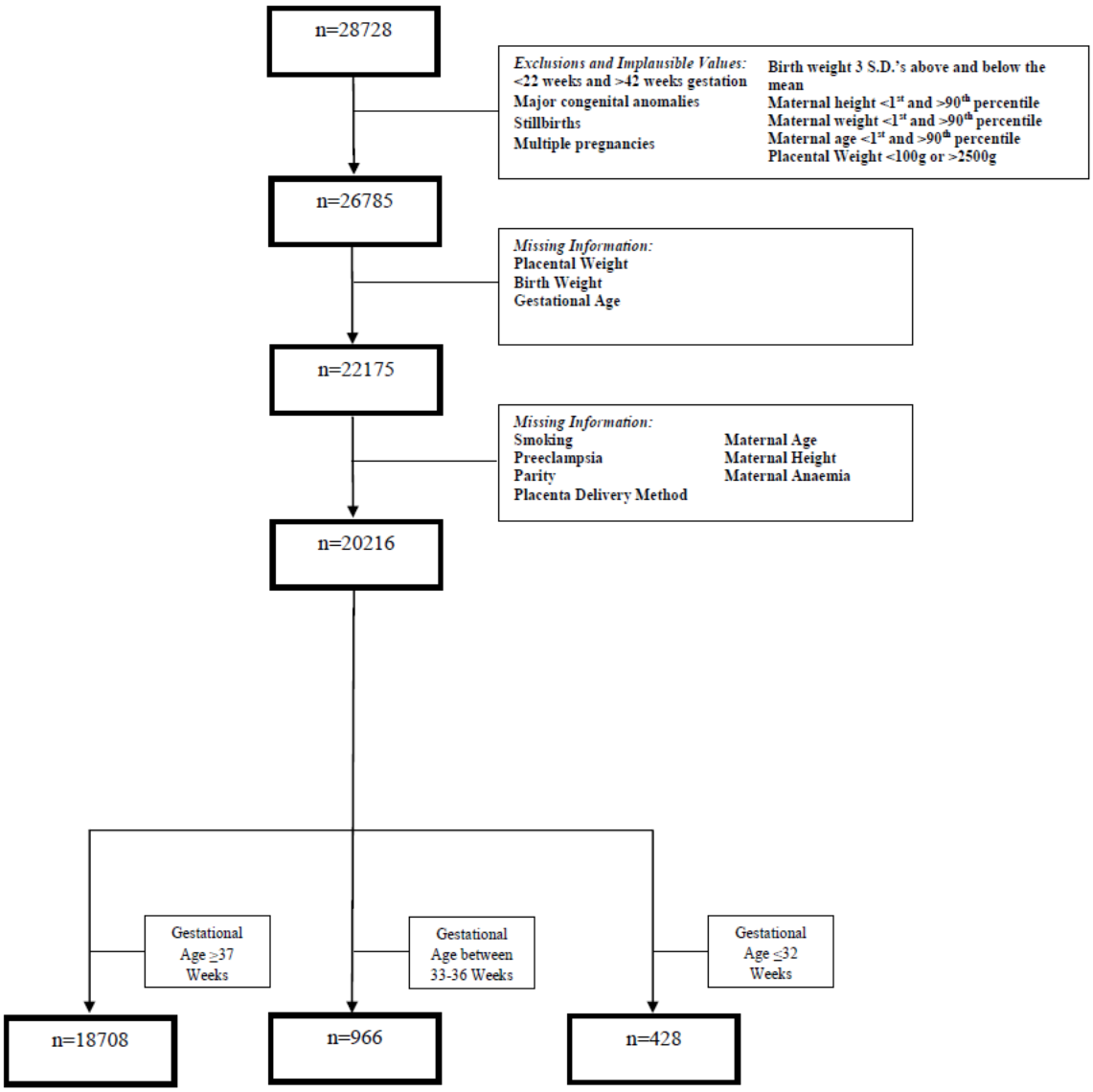


Figure 3.2: Flow chart illustrating the process by which the study population was obtained for Objective 2



CHAPTER 4: POPULATION BASED PLACENTAL WEIGHT RATIO DISTRIBUTIONS

4.1 Introduction

Placental weight is the most common way to characterize placental growth, and it is a summary of many dimensions of placental growth. The placental weight measurement includes the laterally expanding growth of the chorionic disc and arborization of the villous and vascular nutrient exchange surface, which is reflected in the increasing thickness of the chorionic disk. The expansion of the chorionic plate, beginning early in pregnancy, is the principle determinant of placenta transfer capacity to facilitate the genetic growth potential of the conceptus.[1]

Fetal growth depends on placental growth. Fetal growth restriction (FGR) is the failure of a fetus to reach his/her biological growth potential, most probably due to a pathological slow down in the fetal growth rate. Small birth weight for gestational age (SGA) is widely used as a statistical indicator of FGR, since FGR is not measurable. SGA is defined as birth weight < 10^{th} percentile for gestational age and sex based on a population standard.[2] Placental weight is lower in SGA infants than in average for gestational age (AGA) and large for gestational age infants (LGA).[3,45]

The placental weight ratio (PWR) is a common measure of the balance between placental and fetal growth. The PWR is defined as the placental weight divided by the birth weight, and decreases across gestation as the placental growth slows and fetal growth accelerates.[6] Placental hypertrophy and reduced fetal growth have been postulated to be an adaptation to maintain placental function in pregnant women with complications such as malnutrition.[7] If this is true, a pregnancy with impaired fetal growth, resulting in a SGA infant, should have an increased PWR compared to those infants who are AGA or LGA.[1,8]

Placental weight and the PWR have been found to be predictive of maternal disease, obstetric outcome, perinatal morbidity and mortality, childhood growth and

development, and fetal origins of adult disease.[9–14] While percentile curves for birth weight are available for a variety of jurisdictions and populations, percentile curves for the PWR are not. Thompson et al.[15] created birth weight to placental weight ratio curves using the Norwegian Birth Registry with all singleton live births in Norway from January 1999 to December 2002 (n= 198, 971). These curves were a significant contribution to the literature. Further, no population curves to date have looked at the differences between SGA and LGA across gestational age. Searching the available literature, we found only one other set of PWR percentile curves in a Canadian population.[6] However, the sample size was small (n=20,309). Also, previous studies that have looked at atypical PWRs have not used a population standard to identify abnormal PWRs.[16–18]

If the pattern of placental growth is associated with differences in the efficiency of placental function, and therefore fetal growth, as reflected in the PWR, this may have physiological implications. Therefore, it would be useful to have standardized curves in order to ascertain normal from abnormal PWR. Accordingly, the first objective of this study was to develop standard curves for the PWR across gestational ages in a population-based birth cohort. Since literature evidence suggests that placental weights differ between SGA, AGA and LGA infants, a second objective was to examine this in order to refine the potential applications of the PWR trajectories. Having the knowledge of the expected norms of PWR will provide a useful standard for further research.

4.2 Methods

The study included all singleton births from St. Joseph's Health Care and Victoria Hospital in London, Ontario between April 1, 2001 and March 31, 2011. The perinatal database provides targeted information on all births occurring at the hospitals. Anomalies (n=881), still births (n=422), and multiple gestations (n=2876) were excluded from the analyses. All remaining singletons were included (n=41,441).

Data in the database were entered from the medical chart, delivery records, and neonatal records by a dedicated research assistant. Placentas and infants were weighed by nursing assistants with an electronic weight scale. Placentas were weighed with

membranes and umbilical cord, including the segment of cord used for cord blood sampling. No attempt was made to remove placental blood before weighing. Placental weight was not collected at both hospitals for the entire duration of the study therefore, there were 13,084 missing values. Missingness for categorical variables is outlined in Appendix L.

Gestational ages of births recorded in the database ranged from 20 to 44 weeks, but only births between 22 and 42 weeks gestation were included in the analyses. Gestational age was truncated to the number of completed weeks based on the recommendations from World Health Organization and International Classification for Disease, and was based on ultrasound or last menstrual period. Birth weight was categorized into SGA, AGA and LGA based on Kramer standards.[19]

Descriptive analyses were performed on all study variables. Implausible values and potential errors were excluded from the analyses. Birth weights above or below the mean by three SD's were removed from the analyses. Placental weights that were ≤100 g or ≥2500g were also excluded from the analyses. Maternal age, maternal height and pre-pregnancy weight were all trimmed at the 1st and 99th percentiles to remove any erroneous values. Any unknown or ambiguous sexes were also excluded from the analyses.

Placental and birth weight distribution curves, and PWR curves, by gestational age were produced stratified by sex. Initially, estimates were restricted to the population who reside in London-Middlesex excluding regional referrals from outside London-Middlesex. This sample, hereinafter referred to as the "city-wide" sample, would be expected to produce estimates with high internal validity because they represent a "whole population" perspective. A second analysis was done in which PWR curves were estimated for the entire sample of births, including referrals from outside London-Middlesex. Inclusion of the referrals would be necessary for later analyses, stratified by fetal size, in order to produce adequate sample sizes at lower gestational ages. The city-wide PWR distributions were compared to the PWR distributions inclusive of referrals in

order to assess their similarity. Finally, the latter sample was used to create PWR distribution curves separately for SGA, AGA and LGA infants, again stratified by sex.

Following the Center for Disease Control and Prevention standards, we created growth charts at the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th percentiles. We used parametric quantile regression with quadratic terms on gestational age. Non-parametric quantile regression was used for the placental and birth weight distributions, but quadratic splines at 22, 32 and 42 weeks gestation were used as opposed to a quadratic term for gestational age. Quantile regression does not impose any parametric assumptions on the response distributions which make it appropriate for the anthropometric measures.[20] Due to the large sample size, the interior point algorithm was used,[21] and resampling was performed using the Markov chain marginal bootstrap.[22]

4.3 Results

The final sample were 21255 males and 20186 females (total n=41,441). Of these, 33582 were residents of London-Middlesex while 7,859 were regional referrals.

The characteristics of the study sample are given in Appendix L. The mean gestational age for the population studied was 38.8 weeks (SD=2.1 weeks), with median and mode, respectively, of 39 and 40 weeks gestation. The mean birth weight was 3,398.6g (S.D=594.8g, minimum 279g, maximum 5,300g). The mean placental weight was 675.67g (SD=161.18, minimum 103 g, maximum 2,095g). The PWR had mean of 0.20 (SD=0.044, minimum 0.023, maximum 1.17). There were 4,259 (7.9%) SGA infants, 43,697 (81.2%) AGA infants and 5,878 (10.9%) LGA infants in the study sample. The distributions of birth weight, placental weight and gestational age can be found in Appendix M.

Placental Weight, Birth Weight and PWR Distributions

Figures 4.1 (a) and (b) present placental weight and birth weight distributions for males and females, respectively. It can be seen that, because these curves are for the last half of gestation, placental growth has to some degree leveled off while fetal growth continues at an accelerated pace. PWR standards for the city-wide population are shown

in Tables 4.1 and 4.2. All of the percentiles reached a statistical significance of $p<0.001$. Tables 4.3 and 4.4 present the PWR standards when inclusion criteria are relaxed to include regional referrals in the sample.

Comparing the city-wide population to the total sample revealed them to be similar, with minute differences presenting themselves at the extreme percentiles at the earlier gestational ages. Furthermore, comparing the 10^{th} and 90^{th} percentiles which are often used as cut-off points revealed almost no differences, even at the earlier gestational ages. The distributions of the PWR curves for the city-wide population are illustrated in Figures 4.2 (a) and (b). A visual presentation of the PWR curves, inclusive of regional referrals, for males and females are shown in Figures 4.3 (a) and (b), respectively.

All of the percentiles reached statistical significance of $p<0.001$. For males, the median PWR is 0.1938 and the mean is 0.1994 (SD=0.0428). For females, the median PWR is 0.1981 and the mean is 0.2038 (SD=0.0446). The PWR decreases as gestational increases and there is more dispersion between the percentiles at earlier gestational ages than at later gestational infants.

In general, the females have higher PWR's than males. The slightly higher PWR in females than in males is consistent across percentiles. For instance, females have slightly higher PWRs at both the 3^{rd} and 97^{th} percentile across all gestational ages than do males. Using the 50^{th} percentile, the range of values between 22 and 42 weeks gestation is 0.2681 for females and 0.2443 for males. Therefore, there is a greater range in values at the mean for females. Furthermore, the ranges for these values are greatest at the highest percentiles. For both males and females, the ranges at the 90^{th} percentile are more than 2 times as wide as at the 10^{th} percentile. At the 10^{th} percentile the ranges for males and females between 22 and 42 weeks gestation are 0.1622 and 0.1728, and the ranges at the 90^{th} percentile for males and females are 0.3514 and 0.4667. Tables 4.3 and 4.4 show the exact values at each gestational age by percentile.

Placental Weight Ratio Distribution Curves Stratified by SGA, AGA and LGA status

PWR distributions for the entire sample, inclusive of regional referrals, were used in an analysis of SGA, AGA and LGA. The proportion with PWRs $<10^{th}$ percentile,

between the 10^{th} and the 90^{th} percentile and $>90^{th}$ percentile are presented in Table 4.5. There are a higher proportion of SGA infants for both males and females in the extreme PWR groups. Furthermore, there are fewer LGA infants in the lowest PWR group. More detailed descriptions and graphics of the SGA and LGA PWR curves can be found in Appendix N with their accompanying tables and diagrams.

The median PWR curves for each of SGA, AGA and LGA are presented in Figures 4.4 (a) and (b). These show graphically how the PWR changes across gestation between SGA, AGA and LGA infants at the median. Specifically, they show that there is a greater dispersion in the PWR in SGA infants than in AGA and LGA infants, especially in the earlier gestational ages. When comparison is made between LGA and AGA infants the AGA infants show more dispersion at the earlier gestational ages than do the LGA infants. It can then be concluded that the dispersion at the earlier gestational ages is greatest in SGA infants than in both LGA and AGA infants.

Furthermore, at the earlier gestational ages both male and female SGA infants have higher PWR's than male and female AGA and LGA infants. The differences in PWR's were the most pronounced at the higher percentiles and at the earlier gestational ages, as shown in Appendix N. SGA infants had much higher PWR's in early gestation than both SGA and AGA infants at the early gestation. On the other hand, LGA infants have lower PWR's at the earlier gestational ages when compared to AGA infants.

However, the PWR's at term gestations are nearly identical in both SGA and LGA infants. In fact, LGA infants have slightly higher median ratios at term than both SGA and AGA infants. Due to the greater dispersion at the earlier gestational ages in SGA infants, the ranges of PWR's between the 22 and 42 week of gestation is higher in SGA infants than the AGA and LGA infants. This range difference is the greatest at the highest percentiles, but the range in PWR's between 22 and 42 weeks at the lower percentiles is also the greatest in SGA infants. Therefore, as gestational age increases the PWR's become more similar between SGA, AGA and LGA infants, yet the PWR is still higher in SGA infants, especially at the higher percentiles.

AGA Placental Weight Ratio Distribution Curves

There are 16,994 males and 16,764 females who met the criteria for classification as AGA. All of the percentiles attained a significance level of $p<0.001$.

Males have a median PWR of 0.1933 and a mean PWR of 0.1990 (SD=0.0424). Females have a median PWR of 0.1977 and a mean PWR of 0.2032 (SD=0.0441). Again, the PWR decreases as gestational increases and there is more dispersion between the percentiles at earlier gestational ages than at later gestational infants.

Figures 4.5 (a) and (b) show the distributions graphically, and Tables 4.6 and 4.7 provide exact PWR values for each of the aforementioned percentiles by gestational age. Using Tables 4.6 and 4.7, it is evident that there is a greater range in PWR's between the 22 and 42 weeks of gestation at the 50^{th} percentile for females than males. The range for males is 0.2507 and 0.2646 for females. The same pattern holds at the extreme values, such as the 10^{th} and 90^{th} percentiles.

4.4 Discussion

The results of this study contribute to the current literature by creating gender-specific PWR percentile curves which will be a useful tool in further research. While PWR is an important indicator of fetal health, there are few population standards for comparison. Compared to the only other available set of PWR percentiles in a Canadian population,[6] our results complement this literature and now provide more precise PWR predictions, particularly at the extreme percentiles, due to our larger sample size.

4.4.1 Comparisons with Previous Research

In this sample of Canadian births, the mean weight of the placentas was 675 g, and the mean PWR was 0.20. Comparing these results with other studies can be confusing because variation in methods of preparation and storage can alter mean placental weights.[23] Benirschke and Kaufman estimate the mean weight of placenta at 38 weeks gestation, without cord and membranes, as 470 g[24]; our figure for term placentas is 675g but includes the cord and membranes after the cord was cut. The Canadian study that used similar sample preparation had a median placental weight of 680g for boys and

668g for girls. The decline in PWR with increasing gestational age seen here is similar to that described by many others.[23,25,26]

Our birth weight curves differ from the Kramer et al.[27] birth weight distributions in that our birth weights are somewhat larger. Our population includes more recent data and it has been demonstrated that, generally birth weights are increasing.[28] This might be expected since we use more recent data and birth weight is increasing over time due to increases in maternal anthropometry, reduced cigarette smoking, and changes in sociodemographic factors.[28] Also, Kramer's curves did not include the Ontario population due to poor data quality[27]; therefore, the characteristics of the study populations are different.

Searching the available literature, we came across a small number of studies that present the relation between placenta weight to birth weight and only two of these reported percentiles curves for the PWR.[6,15] Thompson et al.[15] reported placental percentile curves for a Norwegian population, and Almog et al.[6] presented PWR curves for a Canadian population. Comparison of our results that include regional referrals with Almog's Canadian standards reveals close resemblance between the two populations, such as median 40 week PWRs (0.1938 and 0.19 for males and 0.1981 and 0.20 for females respectively). The differences between PWRs for males and females, which repeat in both studies as well as ours, may reflect different metabolic programming between the sexes. Dombrowski et el.[25] published data on placental weight and placental to birth weight ratio in North American population. However, their study is based on data from 1984 to 1991, over two decades ago, and contained data mostly a black population (81.4%), so the results cannot reasonably be compared.

Our standards also include earlier gestational ages than both of the aforementioned studies. Both of the abovementioned studies have gestational age standards starting at 24 weeks; however, our standards provide estimates at 22 and 23 weeks as well. Comparison of our results to Thompson's are not possible, as he examined the ratio of the birth weight to the placental weight, and our results examined the inverse ratio. However, comparisons of our results inclusive of regional referrals to Almog's

curves reveal very similar standards. Our results have slightly lower PWRs at all gestational ages and percentiles.[6]

The placenta and fetus follow different growth patterns during gestation.[3] The placenta follows an S-shaped growth curve whereas fetal growth follows an exponential pattern in mid pregnancy, with most growth occurring in a linear fashion during the third trimester.[3] In the earlier gestational ages the birth weight is low in comparison to the placental weight as a result of the higher growth rate of the placenta earlier in gestation. Moreover, our placental growth curves show how the majority of placental growth occurs before 33 weeks gestation. This accounts, at least in part, for the higher PWRs at earlier gestations. Previous authors have shown that the placenta responds to the interruption of the fetal villous circulation in the first half of gestation by initiating compensatory hyperplasia.[29] In conclusion, because placental growth occurs at the earlier gestational ages this is where the greatest differentiation of PWRs is expected to be observed.

Of interest, the PWR curves are similar whether inclusive or exclusive of the referral population. This may be because, at earlier gestations, the vast majority of regional births occur in this tertiary referral center. Thus, the lower gestations represent a "whole population". At later gestational ages, where one might expect the referral population to represent a biased sample of higher risk births, the actual numbers contributed by regional referrals are much smaller and thus would not substantially affect the percentile estimates for term and near-term births. Since the larger sample does not exclude regional referrals, it is not speculated to be biased.

Stratification by Fetal Growth Adequacy

This research is also novel in its examination of percentile curves stratified by fetal growth adequacy, specifically focusing upon how PWRs may change across gestational age between SGA, AGA and LGA infants. However, previous studies have indicated that overall, SGA infants have higher PWR's,[3,5] and that SGA infants have a higher proportion of placental weights at both extremes, but none of these studies have

looked at the relationships across gestation or between percentiles.[4,17,30–32] Alternatively, the literature suggests that a higher proportion of LGA infants have placenta weights above the 90th percentile and a lower share of placental weights below the 10th percentile than SGA and AGA infants.[32] Furthermore, PWRs have been found to be the lower in LGA infants than in AGA and SGA infants.[33]

Our curves show that there is a greater dispersion in the PWR in SGA infants than in AGA and LGA infants, especially at the earlier gestational ages. As gestational age advances, the PWRs become more similar between SGA, AGA and LGA infants, yet the PWR is still higher in SGA infants. At the earlier gestational ages across all percentiles the SGA standards are much higher than the AGA standards. Our results agree with the literature, since SGA infants have higher PWRs than their AGA counterparts. The results go beyond what the previous literature indicates, and demonstrate how the PWR differs throughout gestation between SGA and AGA infants between the percentiles. The SGA infants with PWRs within the highest percentiles may represent the group of infants with failed compensation and, therefore, a high PWR. Finally, our results show that, at earlier gestational ages in male infants, LGA infants generally have lower PWRs than AGA infants. This pattern holds true across all percentiles until the 33rd week of gestation, when the LGA and AGA standards become more similar. However, the differences between the LGA and AGA standards are not as pronounced as the differences between the SGA and AGA standards.

The SGA group studied had PWRs that were generally higher than the respective AGA values, whereas values for infants in the LGA groups were not altered, particularly at term. Therefore, the SGA infant can generally be seen as under grown in relation to placental size, suggesting functional rather than size constraints for the placenta.

Salafia et al.[1] showed that an elevated PWR may be an indication of an inefficient placenta with a reduced ability to maintain fetal growth. Indeed Kingdom and Kaufmann[34] report that preplacental or uteroplacental hypoxia with adaptive placental growth is a primary cause for growth restriction at term. However, the nonplacental

chorion and amnion also contribute to overall placental weight, and more so for SGA infants;[26] this may also account, at least in part, for the higher PWR of infants in the SGA group. On the other hand, low PWR's are indicative of an increased efficiency of the placentas of the smaller fetuses, whereas, high PWR's are indicative of a potential failed compensation.[35–41] Therefore, it is suggested that the PWR can be used as a predictor for placental functional efficiency. The literature on this subject concludes that small fetuses have small placentas. Based on these conclusions and the fact that our results show that SGA infants have a higher PWR than AGA and LGA infants, we propose that this may be due to a failed compensation of the placenta in SGA infants.

4.4.2 Study Strengths and Limitations

A major strength of the study is the available sample size. The perinatal database provided a large number of observations with matching placental weight, birth weight and gestational age. This allowed for the creation of accurate standards, and for the resulting percentile curves to be stratified by fetal growth adequacy standard. The internal validity of the study is strong because every birth at St. Joseph's Hospital and Victoria Hospital was captured.

Birth weights vary widely from country to country[27,42] and as such it might be considered appropriate that birth weight percentiles should be based on data from the actual country or at least from a comparable country. This is often not the case and can lead to inappropriate use of the percentiles in a population where the distribution of birth weight is shifted, particularly to the left. Therefore, our results are generalizable to other tertiary care centers in Canada, and possibly the United States of America. Also, the study of placental weight at the time of delivery is a crude measure of placental growth and development. However, when it is collected in a routine manner and related to birth weight, it provides information of biological importance.

4.4.3 Conclusions and Future Directions

These PWR distribution curves make a substantial contribution to the literature, as they indicate how the PWR changes across gestation by percentile for SGA, AGA and LGA infants. The curves that are stratified by fetal growth adequacy are the first of their kind. They demonstrate that PWR declines across gestation by percentile, yet distinctly, they further show that overall the PWRs are higher for SGA than AGA infants, and that the PWRs are lower for LGA infants than for AGA infants. These trends are most pronounced at the highest percentiles (>90th percentile) and at the earlier gestational ages (22-28 weeks).

The PWR distribution curves provide a standard that researchers can apply as a reference standard to identify infants who have abnormal PWRs. Depending on the purpose of the analysis, researchers may chose to use the population distribution curves or may use the AGA curves as their reference population. Identifying infants with high PWRs is important for patient care in both the short and long term. Neonates with a high PWR had increased incidence of low 1-minute Apgar score, require treatment for neonatal jaundice and infection, and respiratory complications.[43] Furthermore, in recent years, birth weight, sometimes in conjunction with placental weight, has been associated with the development of a series of diseases later in life.[9] These analyses have included birth weight, placental weight and even the PWR; however, the relative magnitude of the latter, in terms of percentiles, has not been previously available for all gestational ages in a Canadian population.

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Table 4.1: City-Wide Male Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.2549	0.2769	0.3050	0.3714	0.4333	0.5052	0.5711	0.6556	0.7267
23	0.2443	0.2648	0.2910	0.3520	0.4098	0.4764	0.5377	0.6142	0.6786
24	0.2342	0.2533	0.2776	0.3335	0.3875	0.4491	0.5061	0.5750	0.6330
25	0.2246	0.2423	0.2649	0.3161	0.3664	0.4232	0.4761	0.5380	0.5901
26	0.2154	0.2319	0.2529	0.2995	0.3464	0.3988	0.4479	0.5033	0.5498
27	0.2068	0.2220	0.2415	0.2839	0.3276	0.3758	0.4213	0.4707	0.5121
28	0.1986	0.2127	0.2308	0.2693	0.3099	0.3543	0.3965	0.4404	0.4771
29	0.1909	0.2040	0.2207	0.2557	0.2934	0.3343	0.3734	0.4123	0.4446
30	0.1837	0.1958	0.2113	0.2430	0.2780	0.3157	0.3521	0.3863	0.4148
31	0.1770	0.1882	0.2026	0.2313	0.2638	0.2985	0.3324	0.3626	0.3876
32	0.1708	0.1811	0.1944	0.2205	0.2508	0.2828	0.3145	0.3411	0.3630
33	0.1651	0.1746	0.1870	0.2107	0.2389	0.2686	0.2982	0.3218	0.3410
34	0.1599	0.1686	0.1802	0.2018	0.2281	0.2558	0.2837	0.3047	0.3216
35	0.1552	0.1632	0.1740	0.1940	0.2186	0.2445	0.2709	0.2898	0.3049
36	0.1510	0.1584	0.1685	0.1870	0.2101	0.2346	0.2598	0.2771	0.2908
37	0.1472	0.1541	0.1637	0.1811	0.2029	0.2261	0.2505	0.2667	0.2793
38	0.1440	0.1504	0.1595	0.1761	0.1968	0.2192	0.2428	0.2584	0.2704
39	0.1412	0.1472	0.1560	0.1720	0.1918	0.2136	0.2369	0.2524	0.2642
40	0.1389	0.1446	0.1531	0.1689	0.1880	0.2096	0.2326	0.2485	0.2605
41	0.1371	0.1425	0.1509	0.1668	0.1854	0.2069	0.2301	0.2469	0.2595
42	0.1359	0.1410	0.1493	0.1656	0.1839	0.2058	0.2293	0.2474	0.2611

Table 4.2: City-Wide Female Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.2274	0.2668	0.3011	0.3692	0.4344	0.5427	0.5960	0.6651	0.6891
23	0.2209	0.2565	0.2880	0.3507	0.4115	0.5101	0.5610	0.6256	0.6490
24	0.2146	0.2466	0.2756	0.3332	0.3897	0.4792	0.5277	0.5882	0.6109
25	0.2085	0.2372	0.2638	0.3165	0.3690	0.4499	0.4962	0.5526	0.5748
26	0.2026	0.2282	0.2525	0.3007	0.3495	0.4224	0.4665	0.5190	0.5405
27	0.1969	0.2196	0.2418	0.2858	0.3310	0.3966	0.4386	0.4874	0.5083
28	0.1915	0.2115	0.2318	0.2718	0.3137	0.3724	0.4124	0.4577	0.4779
29	0.1862	0.2038	0.2223	0.2587	0.2975	0.3500	0.3881	0.4300	0.4496
30	0.1811	0.1965	0.2134	0.2465	0.2824	0.3292	0.3655	0.4042	0.4231
31	0.1762	0.1897	0.2051	0.2352	0.2684	0.3102	0.3448	0.3804	0.3986
32	0.1715	0.1833	0.1974	0.2247	0.2555	0.2929	0.3258	0.3586	0.3761
33	0.1670	0.1773	0.1903	0.2152	0.2438	0.2772	0.3087	0.3387	0.3555
34	0.1627	0.1718	0.1838	0.2065	0.2331	0.2633	0.2933	0.3208	0.3369
35	0.1586	0.1667	0.1779	0.1988	0.2236	0.2510	0.2797	0.3048	0.3202
36	0.1547	0.1620	0.1726	0.1919	0.2152	0.2404	0.2679	0.2908	0.3054
37	0.1510	0.1578	0.1679	0.1859	0.2079	0.2316	0.2579	0.2787	0.2926
38	0.1475	0.1540	0.1638	0.1808	0.2018	0.2244	0.2496	0.2686	0.2818
39	0.1442	0.1506	0.1602	0.1766	0.1967	0.2190	0.2432	0.2604	0.2729
40	0.1412	0.1476	0.1573	0.1733	0.1928	0.2152	0.2386	0.2542	0.2659
41	0.1383	0.1451	0.1550	0.1708	0.1900	0.2131	0.2357	0.2500	0.2609
42	0.1356	0.1431	0.1532	0.1693	0.1883	0.2127	0.2346	0.2477	0.2578

Table 4.3: Inclusive of Regional Referrals Male Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.2646	0.2925	0.3127	0.3685	0.4281	0.5069	0.5803	0.6849	0.7777
23	0.2526	0.2783	0.2976	0.3495	0.4052	0.4780	0.5461	0.6405	0.7239
24	0.2413	0.2648	0.2832	0.3314	0.3835	0.4505	0.5136	0.5985	0.6731
25	0.2305	0.2519	0.2696	0.3142	0.3629	0.4244	0.4829	0.5589	0.6252
26	0.2204	0.2398	0.2568	0.2980	0.3435	0.3998	0.4540	0.5216	0.5802
27	0.2108	0.2285	0.2446	0.2827	0.3251	0.3767	0.4268	0.4867	0.5382
28	0.2018	0.2178	0.2332	0.2684	0.3079	0.3551	0.4014	0.4541	0.4991
29	0.1934	0.2078	0.2225	0.2549	0.2917	0.3349	0.3777	0.4240	0.4630
30	0.1855	0.1985	0.2126	0.2425	0.2767	0.3162	0.3557	0.3961	0.4298
31	0.1783	0.1900	0.2034	0.2309	0.2628	0.2989	0.3355	0.3707	0.3996
32	0.1716	0.1821	0.1949	0.2203	0.2501	0.2832	0.3171	0.3476	0.3723
33	0.1655	0.1750	0.1872	0.2106	0.2384	0.2688	0.3004	0.3269	0.3479
34	0.1600	0.1686	0.1802	0.2019	0.2279	0.2560	0.2854	0.3086	0.3265
35	0.1551	0.1628	0.1739	0.1941	0.2184	0.2446	0.2722	0.2926	0.3081
36	0.1507	0.1578	0.1683	0.1872	0.2101	0.2347	0.2608	0.2790	0.2925
37	0.1470	0.1535	0.1635	0.1813	0.2030	0.2262	0.2511	0.2678	0.2800
38	0.1438	0.1499	0.1594	0.1763	0.1969	0.2192	0.2431	0.2590	0.2703
39	0.1412	0.1470	0.1561	0.1722	0.1919	0.2137	0.2369	0.2525	0.2637
40	0.1392	0.1448	0.1535	0.1691	0.1881	0.2096	0.2325	0.2483	0.2599
41	0.1378	0.1434	0.1516	0.1669	0.1854	0.2070	0.2298	0.2466	0.2591
42	0.1370	0.1426	0.1504	0.1657	0.1838	0.2059	0.2288	0.2472	0.2613

Table 4.4: Inclusive of Regional Referrals Female Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.2763	0.2886	0.3266	0.3777	0.4566	0.5596	0.7037	0.8268	0.8995
23	0.2639	0.2759	0.3106	0.3585	0.4312	0.5252	0.6563	0.7691	0.8348
24	0.2522	0.2637	0.2955	0.3402	0.4070	0.4926	0.6114	0.7144	0.7736
25	0.2410	0.2522	0.2810	0.3229	0.3841	0.4618	0.5690	0.6628	0.7159
26	0.2304	0.2412	0.2674	0.3064	0.3625	0.4327	0.5292	0.6142	0.6616
27	0.2203	0.2308	0.2545	0.2909	0.3421	0.4055	0.4919	0.5687	0.6108
28	0.2108	0.2209	0.2424	0.2764	0.3230	0.3801	0.4572	0.5262	0.5635
29	0.2019	0.2117	0.2311	0.2627	0.3052	0.3564	0.4250	0.4867	0.5196
30	0.1935	0.2030	0.2205	0.2499	0.2886	0.3346	0.3953	0.4503	0.4792
31	0.1857	0.1949	0.2107	0.2381	0.2733	0.3145	0.3682	0.4170	0.4422
32	0.1785	0.1873	0.2017	0.2272	0.2593	0.2963	0.3436	0.3866	0.4087
33	0.1718	0.1804	0.1934	0.2172	0.2465	0.2798	0.3215	0.3594	0.3787
34	0.1657	0.1740	0.1859	0.2082	0.2350	0.2651	0.3020	0.3351	0.3521
35	0.1602	0.1681	0.1792	0.2000	0.2248	0.2523	0.2850	0.3139	0.3290
36	0.1552	0.1629	0.1733	0.1928	0.2158	0.2412	0.2705	0.2958	0.3093
37	0.1508	0.1582	0.1681	0.1865	0.2081	0.2319	0.2586	0.2806	0.2931
38	0.1469	0.1541	0.1637	0.1811	0.2017	0.2244	0.2492	0.2686	0.2804
39	0.1436	0.1506	0.1601	0.1766	0.1965	0.2187	0.2424	0.2595	0.2712
40	0.1409	0.1477	0.1572	0.1731	0.1926	0.2148	0.2380	0.2535	0.2653
41	0.1388	0.1453	0.1552	0.1704	0.1900	0.2127	0.2363	0.2506	0.2630
42	0.1372	0.1435	0.1538	0.1687	0.1886	0.2124	0.2370	0.2507	0.2641

Table 4.5: Placenta Weight Ratio Distributions for SGA, AGA & LGA Infants based upon the Inclusive of Regional Referrals Standards

Inclusive of Regional Referrals Standards	Expected %	Males			Females		
		SGA	AGA	LGA	SGA	AGA	LGA
>90th	10%	13.18%	9.74%	9.82%	11.68%	9.66%	11.69%
10-90th	80%	74.42%	80.22%	81.64%	77.56%	80.22%	80.14%
<10th	10%	12.10%	10.04%	8.53%	10.76%	10.12%	8.16%

Table 4.6: Inclusive of Regional Referrals AGA Male Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

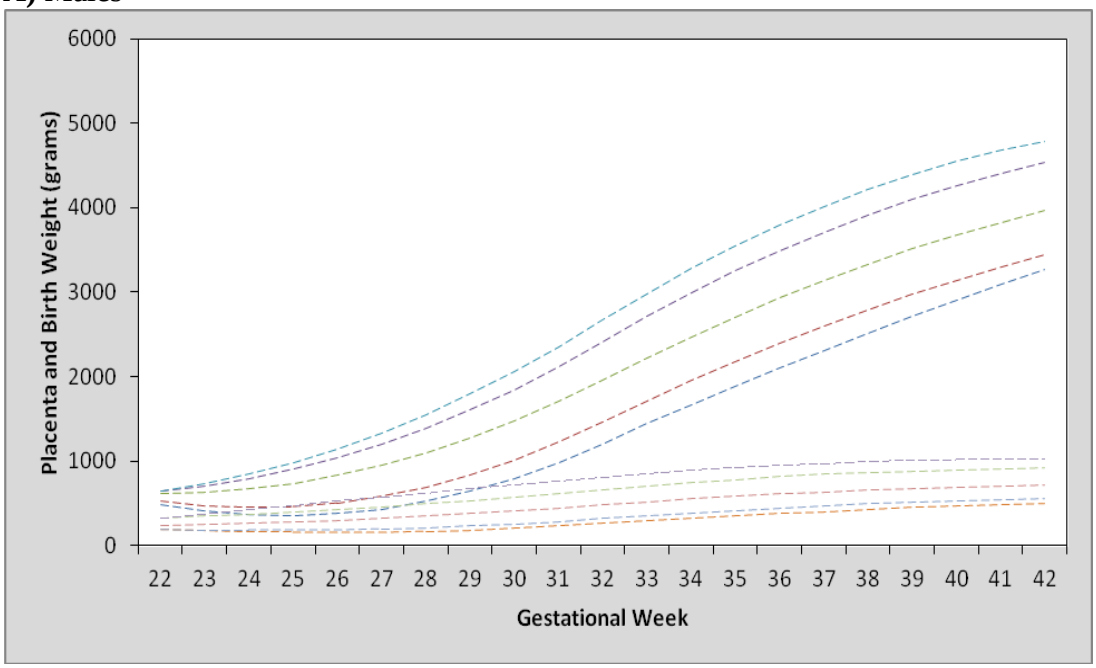
Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.2685	0.2919	0.3167	0.3713	0.4342	0.5047	0.5832	0.6764	0.7461
23	0.2561	0.2779	0.3013	0.3520	0.4106	0.4759	0.5483	0.6330	0.6961
24	0.2443	0.2646	0.2865	0.3336	0.3882	0.4486	0.5152	0.5919	0.6489
25	0.2332	0.2520	0.2725	0.3162	0.3670	0.4228	0.4839	0.5531	0.6043
26	0.2227	0.2400	0.2593	0.2997	0.3469	0.3984	0.4544	0.5166	0.5624
27	0.2127	0.2287	0.2468	0.2842	0.3279	0.3754	0.4268	0.4824	0.5232
28	0.2034	0.2182	0.2351	0.2696	0.3102	0.3539	0.4009	0.4505	0.4867
29	0.1947	0.2083	0.2241	0.2560	0.2935	0.3339	0.3769	0.4210	0.4528
30	0.1867	0.1991	0.2139	0.2433	0.2781	0.3153	0.3547	0.3937	0.4217
31	0.1792	0.1905	0.2045	0.2316	0.2638	0.2981	0.3343	0.3687	0.3932
32	0.1724	0.1827	0.1958	0.2208	0.2507	0.2824	0.3157	0.3460	0.3675
33	0.1661	0.1756	0.1878	0.2110	0.2388	0.2682	0.2989	0.3256	0.3444
34	0.1605	0.1691	0.1806	0.2021	0.2280	0.2554	0.2839	0.3075	0.3240
35	0.1555	0.1634	0.1742	0.1942	0.2183	0.2440	0.2707	0.2917	0.3063
36	0.1511	0.1583	0.1685	0.1872	0.2099	0.2341	0.2594	0.2781	0.2913
37	0.1473	0.1539	0.1636	0.1812	0.2026	0.2257	0.2499	0.2669	0.2789
38	0.1442	0.1502	0.1594	0.1761	0.1965	0.2186	0.2421	0.2580	0.2693
39	0.1416	0.1472	0.1560	0.1719	0.1915	0.2131	0.2362	0.2514	0.2623
40	0.1397	0.1449	0.1534	0.1688	0.1877	0.2090	0.2321	0.2471	0.2581
41	0.1384	0.1432	0.1514	0.1665	0.1850	0.2063	0.2299	0.2451	0.2565
42	0.1377	0.1423	0.1503	0.1653	0.1836	0.2051	0.2294	0.2454	0.2576

Table 4.7: Inclusive of Regional Referrals AGA Female Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.2763	0.2848	0.3235	0.3729	0.4526	0.5495	0.7036	0.7643	0.8835
23	0.2639	0.2726	0.3078	0.3542	0.4276	0.5160	0.6562	0.7136	0.8207
24	0.2522	0.2609	0.2929	0.3365	0.4040	0.4843	0.6114	0.6654	0.7612
25	0.2410	0.2497	0.2787	0.3196	0.3815	0.4544	0.5690	0.6200	0.7050
26	0.2304	0.2391	0.2653	0.3037	0.3603	0.4262	0.5292	0.5771	0.6522
27	0.2203	0.2291	0.2526	0.2886	0.3403	0.3997	0.4919	0.5368	0.6027
28	0.2108	0.2195	0.2407	0.2744	0.3215	0.3749	0.4572	0.4992	0.5566
29	0.2019	0.2106	0.2295	0.2610	0.3040	0.3520	0.4249	0.4642	0.5138
30	0.1935	0.2021	0.2192	0.2486	0.2877	0.3307	0.3952	0.4319	0.4744
31	0.1857	0.1942	0.2095	0.2371	0.2726	0.3112	0.3680	0.4022	0.4383
32	0.1785	0.1869	0.2007	0.2264	0.2587	0.2934	0.3434	0.3750	0.4055
33	0.1718	0.1801	0.1926	0.2166	0.2461	0.2774	0.3212	0.3506	0.3761
34	0.1657	0.1738	0.1852	0.2077	0.2347	0.2632	0.3016	0.3287	0.3501
35	0.1602	0.1681	0.1786	0.1997	0.2246	0.2506	0.2845	0.3095	0.3273
36	0.1552	0.1629	0.1728	0.1926	0.2157	0.2398	0.2699	0.2929	0.3080
37	0.1508	0.1583	0.1677	0.1863	0.2080	0.2308	0.2579	0.2789	0.2919
38	0.1469	0.1542	0.1634	0.1810	0.2015	0.2235	0.2484	0.2676	0.2792
39	0.1436	0.1506	0.1599	0.1765	0.1963	0.2180	0.2413	0.2588	0.2699
40	0.1409	0.1476	0.1571	0.1729	0.1923	0.2142	0.2369	0.2527	0.2638
41	0.1388	0.1451	0.1551	0.1702	0.1895	0.2121	0.2349	0.2493	0.2612
42	0.1372	0.1432	0.1538	0.1684	0.1880	0.2118	0.2355	0.2484	0.2618

Figure 4.1: City-Wide Placenta and Birth Weight Percentile Distributions by Gestational Age

A) Males



B) Females

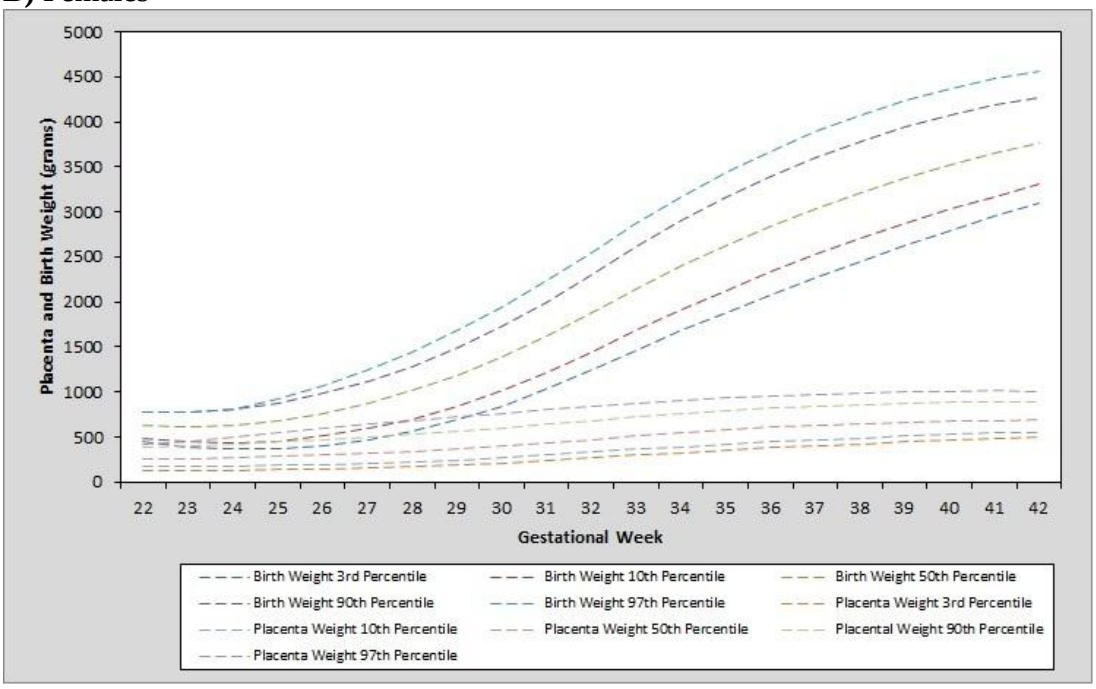
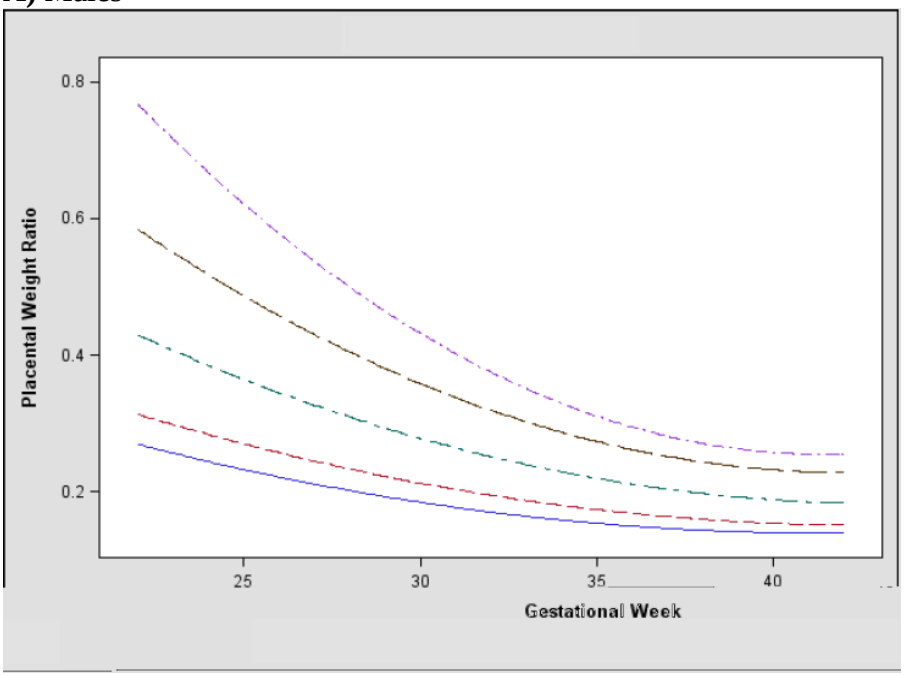


Figure 4.2: City-wide Placental Weight Ratio Distributions by Gestational age

A) Males



B) Females

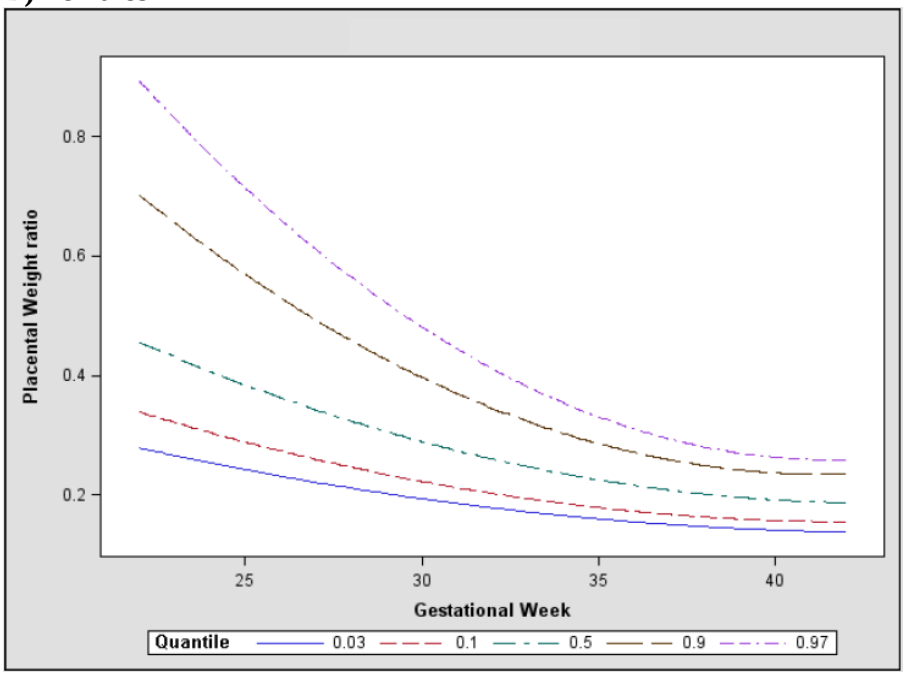
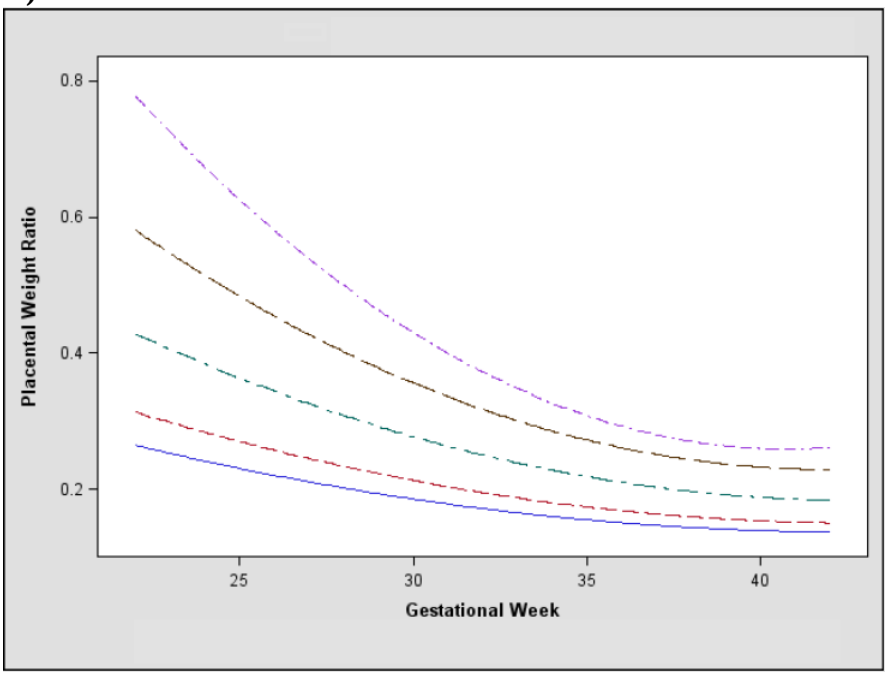


Figure 4.3: Inclusive of Regional Referrals Placental Weight Ratio Distributions by Gestational Age

A) Males



B) Females

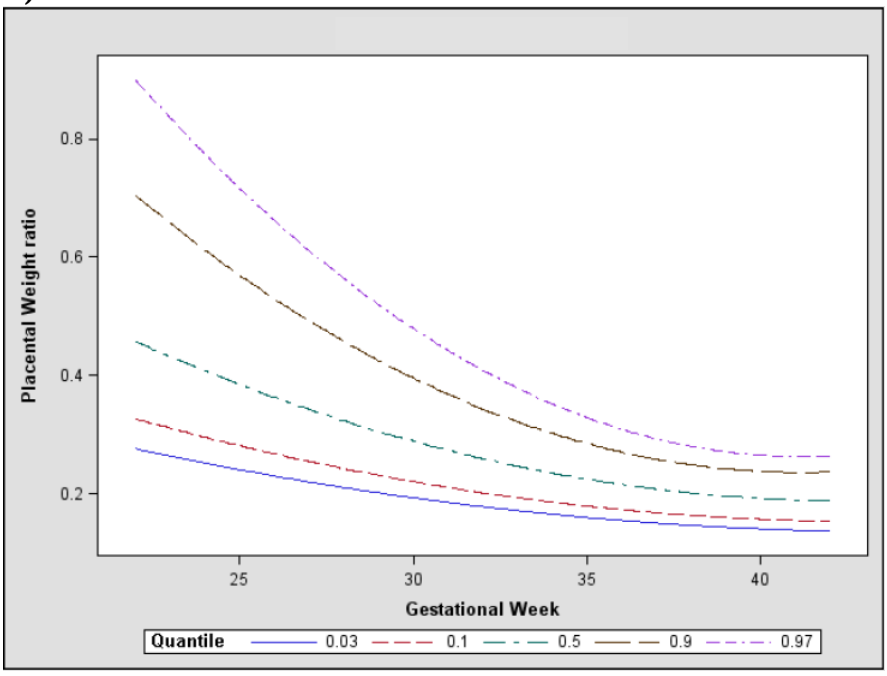
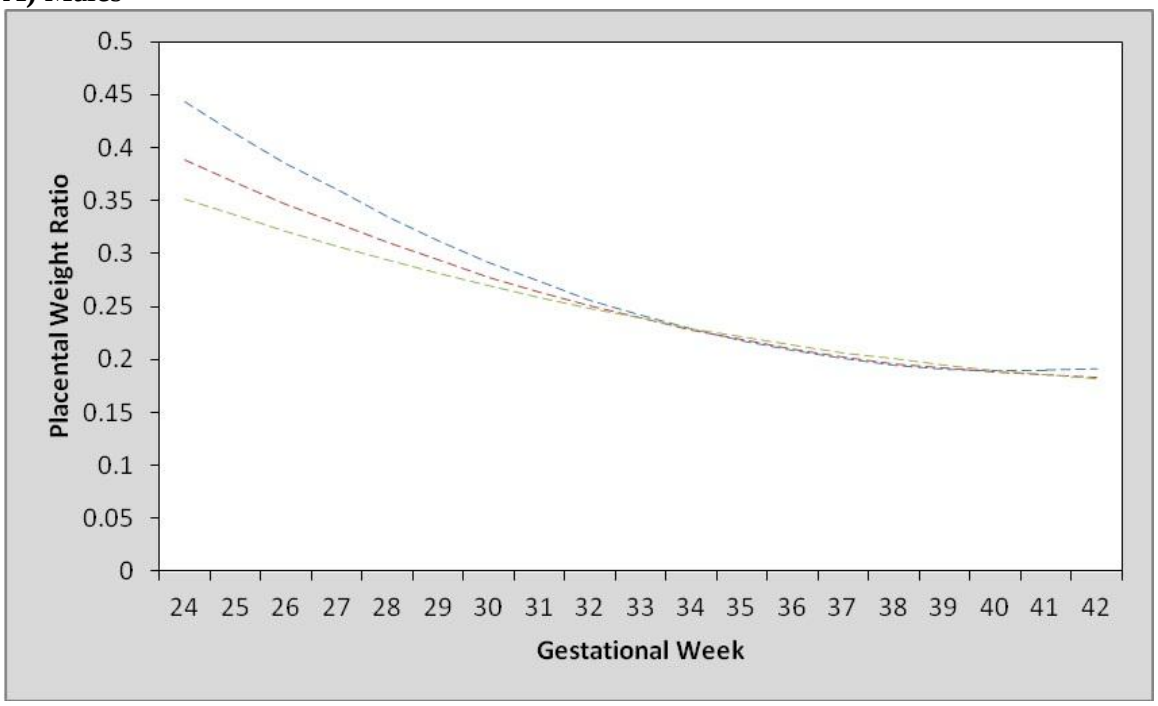


Figure 4.4: Inclusive of Regional Referrals SGA, AGA and LGA Median Placental Weight Ratio Distributions by Gestational Age

A) Males



B) Females

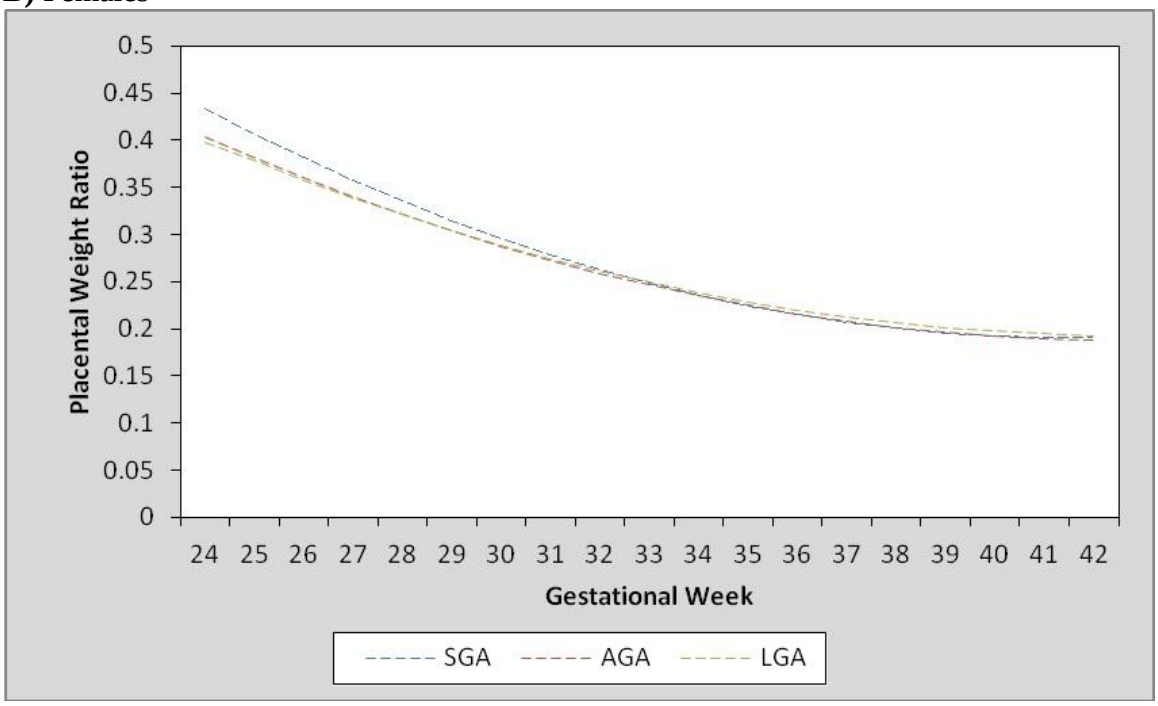
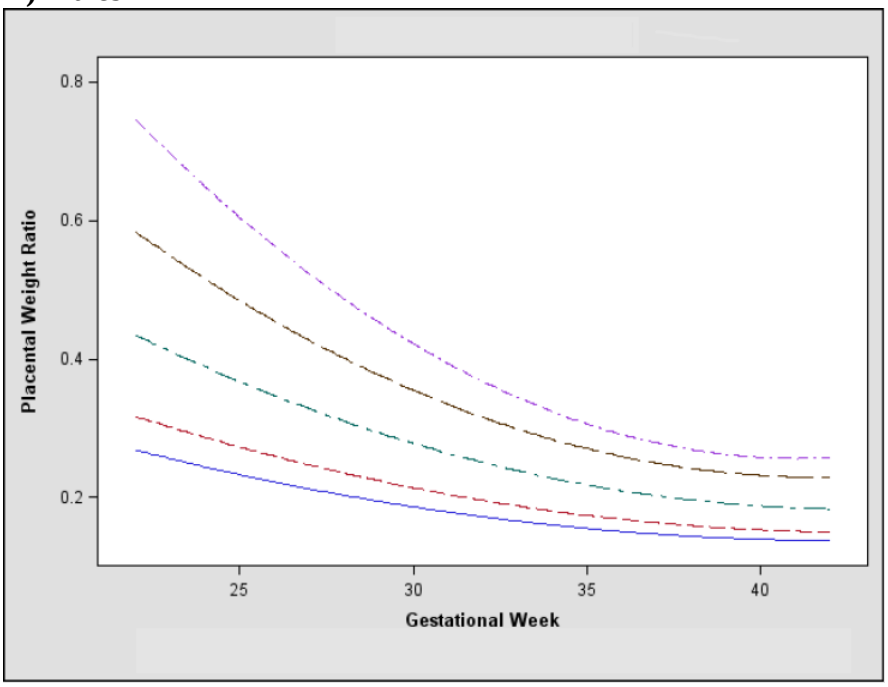
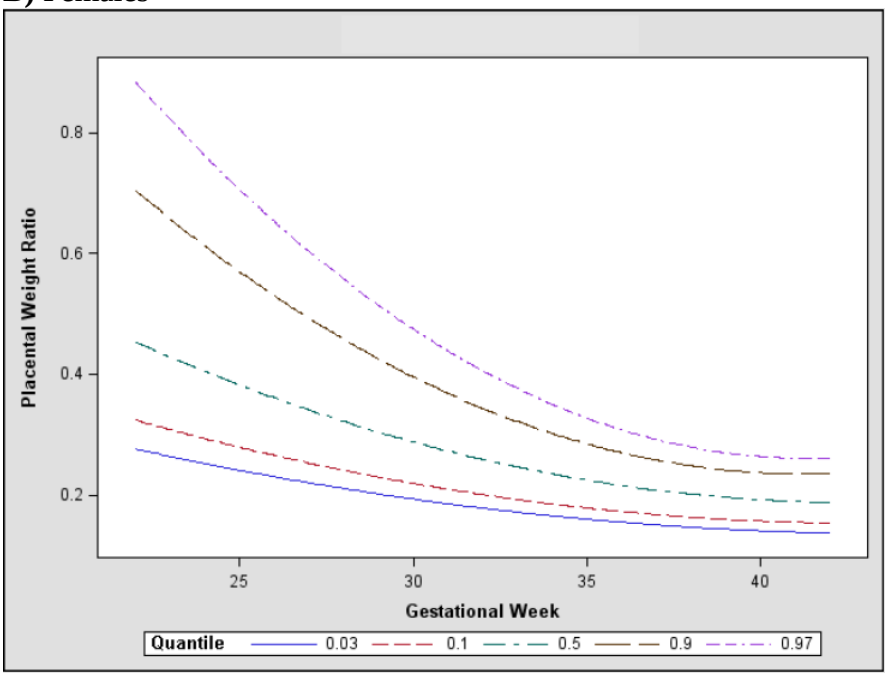


Figure 4.5: Inclusive of Regional Referrals AGA Placental Weight Ratio Distributions by Gestational Age

A) Males



B) Females



CHAPTER 5: DETERMINANTS OF PLACENTAL WEIGHT RATIOS

5.1. Introduction

The placental weight ratio (PWR) is a measure of the balance between fetal and placental growth. The PWR is defined as the placental weight divided by the birth weight, and it decreases across gestation as the placenta matures, concurrent with increased transport capacity and corresponding increases in fetal weight.[4] Recent reports indicate that placental weight and the PWR are predictive of maternal disease, obstetric outcome, perinatal morbidity and mortality, and childhood growth and development.[1–6]

It is postulated that in situations involving complications such as preeclampsia, a disproportionally large placental indicative of placental hypertrophy occurs and have been postulated to be an adaptation to maintain placental function, though the adaptation is insufficient and fetal growth is impacted. If this is true, a pregnancy with impaired fetal growth, resulting in a small for gestational age (SGA) infant, should have an increased PWR compared to those infants who are appropriate for gestational age (AGA) or large for gestational age (LGA).[5,6] However, other maternal factors and pregnancy complications can also alter the PWR, but have been minimally studied in the epidemiologic literature.

Therefore, the relationship of the PWR to maternal baseline factors and pregnancy complications needs to be explored. Preeclampsia, intrauterine growth restriction (IUGR), and placental abruption, conditions that constitute ischemic placental disease (IPD), have been shown to exert their effects differently in term infants than in preterm infants, potentially resulting from different pathophysiological mechanisms.[7] Therefore, the purpose of this large-scale population study is to evaluate the various risk factors associated with atypical PWRs in (a) term infants, (b) infants born between 32 and 37 weeks gestation and (c) infants born between 21 and 33 weeks gestation.

5.2. Methods

The study included all singleton births from St. Joseph's Health Care and Victoria Hospital in London, Ontario between June 1, 2006 and March 31, 2011. The time window was selected based on a start date for which all of the covariates of interest were collected in the database. The perinatal database provides specific information on all births occurring at the hospitals. The data are prospectively entered from the medical chart, delivery records, and neonatal records by a committed research assistant. For the time window examined in the present study, the sample available was after exclusion of congenital anomalies (n=414), stillbirths (n=193), and multiple gestations (n=1,374), as well as exclusion of those for whom placental weight was missing (n=4,812). The latter occurred because placental weight was not collected at both hospitals for the entire duration of the study window. Gestational ages of births recorded in the database ranged from 20 to 44 weeks, but only births between 22 and 42 weeks gestation were included in the analyses.

Placentas and infants were weighed by nursing assistants with an electronic weight scale immediately after delivery. The placentas were weighed with the membranes and umbilical cord, including the segment of cord used for cord blood sampling, and no attempt was made to remove placental blood before weighing.

Descriptive analyses were carried out on all study variables. Implausible values and potential errors were excluded from the analyses. Birth weights above or below the mean by three SD's were removed from the analyses. Placental weights that were ≤100 g or ≥2500g were also excluded from the analyses. Maternal age, maternal height and pre-pregnancy weight were all trimmed at the 1^{st} and 99^{th} percentiles to remove any erroneous values. Any unknown or ambiguous sexes were also excluded. For analysis, gestational age was truncated to the number of completed weeks based on the recommendations from World Health Organization and International Classification for Disease, and was based on ultrasound or last menstrual period. Birth weight was categorized into SGA, AGA and LGA based on Kramer standards.[8]

Univariable and multivariable analyses were stratified by gestational age categories of ≥ 37 weeks, 32-37 weeks and <32 weeks. This stratification was based on both conceptual and statistical grounds, since research has identified different risk factors for placental and fetal growth disturbances at different gestational ages. Thus, stratification will provide more meaningful information on how various risk factors influence both placental and fetal growth, as captured in the PWR, at different points in gestation. Statistically it was anticipated that there would therefore be interaction between factors influencing PWR and gestational age category. Stratification provides an opportunity to evaluate this interaction within clinically meaningful gestational age categories.

Multivariable analysis of the factors associated with a PWR <10^{th} percentile or >90^{th} percentile was carried out using multinomial logistic regression with chunked entry of variables entered in order of temporality, based on a hypothesized conceptual model. During the model building process, variable pruning was conducted using p-to-remove of <0.20. For the final model, this was adjusted to $p<0.05$. PWR between the 10^{th} and 90^{th} percentile was the reference group. The chunks were: baseline variables (parity, smoking status, maternal asthma, age, BMI, maternal height); mid-pregnancy variables (gestational diabetes, preeclampsia); placental and cord complication variables (placental previa and abruption, cord complications); and late pregnancy and postpartum variables (gestational weight gain, birth weight category, anaemia, placental delivery).

5.3. Results

The final sample were 10,404 males and 9,812 females (total n=20216). The mean gestational age for the population studied was 38.8 weeks (SD=2.1 weeks). There were 17,838(80.44%) infants with PWRs between the 10^{th} and 90^{th} percentile, 2,084 (9.40%) infants with PWRs ≤10^{th} percentile, and 2,253 (10.16%) of infants with PWRs ≥90^{th} percentile. Infants with a PWR between the 10^{th} and the 90^{th} percentile were the reference category for all of the analyses.

The mean age for participants was 29 years and the mean height is 64.8 inches. Approximately 18% of the population smoked, 3.0% had preeclampsia, 3.5% had anaemia before delivery, 4.1% had gestational diabetes, 30% had an underweight pre-pregnancy BMI, 13% had an overweight BMI and 9% had an obese pre-pregnancy BMI, and 31% had some form of an umbilical cord complication. The distributions of these risk factors by gestational age category are outlined in Table 5.1.

Two of the key covariates that showed an association with an atypical PWR, were smoking and preeclampsia. These two factors were tested to determine if they had significant interactions with gestational age category. At a significance level of $p<0.05$, both smoking and preeclampsia had significant interactions with gestational age category. The results of the interactions can be found in Appendix O.

The results of the univariable and multivariable regression are presented in Tables 5.2 and 5.3 respectively by gestational age category. The results outlining each model in the model building process can be found in Appendix P.

For infants born at ≥37 weeks gestation, factors associated with a reduced risk of PWR<10^{th} percentile were: multiparity, smoking, abnormal BMI, gestational diabetes, an umbilical cord around the neck or body, a knot in the cord, or a prolapsed or lacerated cord, and being LGA. Factors associated with an increased risk of PWR<10^{th} percentile were: a short, 2-vessel or velamentous umbilical cord insertion, SGA infants, and any assisted placental delivery methods increased the odds of a PWR <10^{th} percentile. Conversely, the risk of PWR >90^{th} percentile was higher for: multiparity, smoking, abnormal BMI, preeclampsia, placental abruption, a cord around the neck or body, a knot in the cord, or a prolapsed or lacerated cord, both SGA and LGA infants and maternal anaemia. Findings that were significant in the univariable, but fell out of statistical significance when controlled for other factors in the multivariable model was increased effect of a PWR<10^{th} percentile that resulted from increasing maternal height. Finally, maternal age <21 year of age increased the odds of a PWR >90^{th} percentile in the univariable, but was no longer significant in the multivariable.

For infants born between 32 and 37 weeks gestation, multiparity attenuated the odds of a PWR <10th percentile. Alternatively, factors associated with all increased the odds of a PWR >90th percentile were: multiparity, smoking, preeclampsia, placental abruption, a cord around the neck or body, a knot in the cord, or a prolapsed or lacerated cord, a short, 2-vessel or velamentous umbilical cord insertion, and maternal anaemia.

Turning attention to the infants born at ≤32 weeks gestation, factors associated with attenuated odds of a PWR<10th percentile were: multiparity, placental abruption, and manual placental delivery. Conversely, factors associated with increased odds of a PWR<10th percentiles were: increasing maternal height, short, 2-vessel or velamentous umbilical cord insertion and retained placental delivery. Multiparity, increasing maternal height and placental previa all increased the odds of a PWR >90th percentile. A finding that was significant in the multivariable but fell out of significance in the univariable was preeclampsia's effect on increasing the odds of a PWR <10th percentile

5.4 Discussion

5.4.1 Main Findings and Implications

The results will be presented in the context of preplacental, uteroplacental, postplacental, and carbon monoxide hypoxia, as well as IPD, umbilical cord and placental complications and key baseline characteristics, for the discussion.

Baseline Factors

The majority of the baseline factors were associated with a hypertrophic growth response of the placenta in relation to birth weight.

High BMI has been identified as predictor of a higher PWR by some investigators,[9–11] but an elevated ratio has not been previously associated with an underweight BMI group.[12] We found that the PWRs are elevated at BMIs both above and

below the normal BMI range in term infants. Physiological research shows that maternal body compositions are associated with changes in the ability of the placenta to transfer maternal nutrients to the fetoplacental compartment through increases in the placental System A amino acid transporter. Furthermore, System A activity was found to be higher in placentas which were large in relation to birth weight.[13] Increased awareness on the importance of health pre-pregnancy weight, and thereby infants at high risk for elevated PWRs, would have implications for the health care system, the health of the mother and the health of the child.

The literature shows that a positive association exists both between placental weight[9,14,15] and birth weight with parity. [16] Our results indicate that throughout all gestational age categories, being multiparous increases the odds of having a PWR≥90th percentile, and the effect is most pronounced in the infants born at ≤32 weeks. The physiological role of the placenta in mediating the effects of parity needs further investigation.

Results are divided on the proposed association between maternal age and placental weight.[14,17] However, SGA is the most common among pregnancies at both extremes of reproductive bearing age.[18,19] Increasing maternal height is associated with both an increased odds of a PWR ≥90th and a PWR ≤10th percentile in infants born at the earliest gestational ages. Height is an non-modifiable characteristic due to its genetic contribution.[20] Other studies have looked at the effect of maternal height on both birth and placental weight, and have found a positive association[9,22]; yet, no other study to date, that we are aware of, has examined the relationship between maternal height and the PWR.

Ischemic Placental Disease

IPD has been shown to exert its effects differently in term and preterm infants[7,23]. Ananth et al.[23] have shown that among infants with IPD the frequency of SGA is higher in term than in preterm infants. Interestingly, SGA was only significantly associated with

atypical PWRs in term infants. Ananth et al.[23] have also shown that IPD in preterm birth is more likely to include the mother and the fetus through not only SGA, but also the addition of preeclampsia and placental abruption. Preeclampsia and placental abruption share a significant number of risk factors which supports the proposed common underlying pathophysiology.[24] Our results have shown that preeclampsia and placental abruption increase the odds of a PWR $\geq 90^{th}$ percentile in the highest two gestational age categories. Moreover, the effect of placental abruption and preeclampsia in infants born between 32 and 37 weeks on a PWR $\geq 90^{th}$ percentile is slightly increased compared to term infants.

Preplacental Hypoxia

Preplacental hypoxia, a reduction in maternal blood oxygen content, occurs when the placenta and fetus become hypoxic due to conditions such as maternal asthma and maternal anaemia.[25] Many researchers have noted that placentas tend to be heavy in pregnancies complicated by both severe and mild maternal anaemia, with the fetus often being small, and therefore the PWR increased.[14,22,26–29] In term infants, maternal anaemia, were associated with amplified odds of having a PWR$\geq 90^{th}$ percentile. The increased size of the placenta has been understood as a compensatory mechanism to overcome the lack of oxygen in the maternal blood, as well as the increased trophoblastic proliferation and placental angiogenesis that results from anaemia.[30] In response to the lack of oxygen, the extravillous trophoblast of the placenta bed shows an increased depth of invasion and the villi appear hypercapillarized.[31]

Uteroplacental Hypoxia

Uteroplacental hypoxia occurs when normally oxygenated maternal blood has restricted entry into the uteroplacental tissues due to either occlusion or failed trophoblast invasion of the uteroplacental arterioles. Uteroplacental hypoxia represents late onset growth restriction with preserved end diastolic flow volume, and term preeclampsia.[25] Both low and high placental weight has been shown to be associated with term

preeclampsia.[32] Our results exhibit that individuals with preeclampsia who deliver an infant at term have increased odds of a PWR ≥90th percentile. These results are congruent with current literature which shows that the PWR is often increased in pregnancies that are complicated with preeclampsia.[33,34] This suggests that there is compensatory growth of placental villi in an attempt to overcome an unfavourable maternal environment.[35,36] However, our results do not show increased odds for having a PWR ≤10th percentile, thereby indicating a potentially smaller placenta. This may be the result of, at least in part, that we do not have the timing of diagnosis for preeclampsia. Nevertheless, it has been suggested that the majority of pregnancies with preterm preeclampsia do result in a preterm delivery.[37]

It has been found that low placental weight is strongly associated with preterm preeclampsia.[32,38] Interestingly, in the univariable analysis preeclampsia's effects in terms infants showed a protective effect on having a PWR≤10th percentile and a strengthened effect on having a PWR≥90th percentile. On the other hand, infants born between 32 and 37 weeks only had increased odds of having a PWR≥90th but were not significantly protected against a PWR≤10th. Finally, in infants born at ≤32 weeks both the odds of having a PWR≥90th and ≤10th were increased, but they were only significantly increased for having a PWR≤10th. Therefore, the direction of the effect changed as the pregnancy progressed. This may represent the two different forms of preeclampsia that have been proposed.[39] However, these effects fell out of significance in the multivariable analysis.

Postplacental Hypoxia

Postplacental hypoxia is when oxygenated maternal blood enters the intervillous space at a normal or reduced rate, but a defect in fetoplacental perfusion prevents the fetus from receiving sufficient oxygen.[25] We had focused the discussion of postplacental hypoxia on gestational diabetes, as it is the only risk factor with this hypoxia type available in the database. Placental adaptations in mothers with pre-gestational diabetes resemble those adaptations seen in other postplacental hypoxia conditions. It has been noted by several authors that the placentas from women with gestational diabetes often

weigh more.[40–45] However, the literature is inconclusive on the effect of gestational diabetes on the PWR.[41,46] In our highest gestational age categories, gestational diabetes was associated with increased odds of a PWR ≥90th and protective against a PWR ≤10th percentile. Increased levels of haemoglobin and erythropoietin provide evidence that fetuses in mothers with pre-diabetes are hypoxic. The literature proposes that the surface and exchange areas are enlarged as a result of the hypoproliferation and hypervascularization in gestational diabetes.[47] Therefore, the maternal placental oxygen supply is reduced, and the fetal oxygen demand is increased.[48,49] This phenomenon could be explained by aerobic metabolism which is stimulated by fetal hypersinsulinemia which can result in reduced trophoblast proliferation. The low oxygen levels up regulate transcriptional synthesis of leptin, VEGF and fibroblast growth factor which promotes placental endothelial cell proliferation. The result is enhanced vascularisation of the placenta.[50,51]

Carbon Monoxide Hypoxia

Maternal smoking presents itself as carbon monoxide hypoxia. While this seems similar to preplacental hypoxia, and the changes in fetal capillaries and peripheral villi do reflect the effects in preplacental hypoxia, the morphology and oxygen diffusion conductance's are not mirrored.[52,53] Cigarette smoking is associated with a decreased fetal weight. The few studies that have looked at maternal smoking and placental weight have found conflicting results,[14,54–58] as are the results on the role of smoking on the PWR.[9,54,56] Our results indicate that in term infants and infants born between 32 and 37 weeks gestation, smoking increases the odds of having a PWR ≥90th percentile and attenuates the odds of having a PWR ≤10th percentile. When a mother smokes during pregnancy, the placenta and fetus become hypoxic because of a reduction of oxygen content within the maternal blood along with an increased vascular resistance on the fetal side of the placenta. These conditions result in reduced intraplacental oxygen content, predominately branching angiogenesis and reduced vascular impedance. The increase in branching angiogenesis and thereby reduced vascular impedance is an adaptive

mechanism to the hypoxic state. This mechanism is associated with excessive placental weight.[59]

The number of women who smoke during pregnancy is high despite current recommendations for mothers to quit. Targeting women who smoke during pregnancy and aiding them in quitting may be an effective strategy to reduce decreases in birth weight accompanied by increases in placental weight.

Placental and Umbilical Cord Complications

Any type of force that compresses umbilical cords may lead to diminished blood flow in umbilical vessels and subsequent fetal hypoxia or circulatory compromise. Mechanical cord compression can be caused by cord entanglements and cord prolapse, or it may occur from an abnormal configuration of the cord such as true knots, hypercoiling, abnormally short or long cords, abnormal cord insertions, or strictures.[60] These complications are often associated with decreased fetal weight, and both marginal and velamentous cord insertion are associated with an increased placental weight and reduced metabolic efficiency.[61–63] In addition, a single umbilical artery is also associated with a reduced placental weight.[61] Furthermore, abnormal cord insertion has also been found to be associated with a high PWR.[64] Our results show that a short, 2-vessel or velamentous cord insertion are associated with increased odds of a PWR $\geq 90^{th}$ percentile in infants born between 32 and 37 weeks, and increased odds of a PWR $\leq 10^{th}$ percentile in terms infants and infants born $\leq$32 weeks. On the other hand, a cord around the neck or body, knot in the cord, prolapsed or lacerated cord is also associated with a PWR $\geq 90^{th}$ percentile in all infants born at >32 weeks.

Literature on this topic indicates that some placental factors, such as placenta abruption, placenta previa and antepartum hemorrhage are not individually associated with placental weight,[61] but as a group are associated with a decreased PWR.[12] Our results partially disagree with these findings. We found no association between placental

previa and the PWR, but we did note that placental abruption strengthened the odds of having a PWR $\geq 90^{th}$ percentile.

5.4.2 Strengths and Limitations

The perinatal database has a number of attributes, which prompted its use in this study. A major strength of the study is the available sample size. This study is strong due to the quality and comprehensive nature of the data. The internal validity of the study is strong because every birth at St. Joseph's Hospital and Victoria Hospital was captured. The results will be important for both obstetricians and neonatologists managing high-risk pregnancies and infants with extreme birth and placental weights.

This research is novel in its ability to combine the proposed physiological mechanisms along with a theoretic framework to examine the relationships between various risk factors and their associations with atypical PWRs. The strong theoretical framework, based on biologically plausible mechanistic literature, combined with epidemiological literature provides a strong base for this study. This approach also allows the complexity of the relationships that exist between factors to be conserved and provides an understanding of how these factors relate within this population.

Like other studies that use administrative databases, this study was unable to assess a few covariates that may influence the PWR such as residing at high altitude and ethnicity. Future studies which can incorporate this information may be useful. However, residing at high altitude is a form of preplacental hypoxia which was evaluated by other variables, and is not believed to be a variable of great significance for many women living in the region. Ethnicity has been shown to influence the PWR in previous studies, but the effect was small.[11,14]

We were limited by the data available in the database, so the available variables are categorized into their respective sections in the discussion. However, we did not have

uterine artery Doppler's or timing of preeclampsia, so we speculated based on the scope of our data.

Height and weight data contributing to the calculation for pre-pregnancy came from variable sources, including self-report, therefore misreporting may have influenced the accuracy of BMI. We speculate it may have produced an underestimate in BMI. The situation is similar for smoking because women sometimes fail to report such behaviours.

Although quality control measures are in place, human error was expected. Any missing data however was expected to be missing completely at random. A more detailed description of missing data with regards to placental weight can be found in Appendix Q.

5.4.3 Conclusions and Future Directions

Our results propose that adverse obstetric conditions are associated with either placental growth restriction or placental hypertrophy in relation to birth weight, and even both, based on gestational age at delivery. The majority of the risk factors assessed resulted in increased odds of a PWR $\geq 90^{th}$ percentile. This suggests that the placenta may have particular compensatory responses to maternal obstetric conditions, each with a distinct pathophysiologic mechanism, but similar PWR outcome. Further research is justified to elucidate the biological mechanisms underlying the associations between anemia, gestational diabetes, hypertensive disease, maternal pre-pregnancy BMI, and umbilical cord complications with abnormal placental growth relative to fetal growth.

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Table 5.1: Descriptive Statistics of Risk Factors by Gestational Age Category

Predictor Variables (Binary/Categorical)		≥37 Weeks Gestation	Between 32-37 Weeks Gestation	≤32 Weeks Gestation
TOTAL		24713	1370	987
Parity	0	10808(43.74%)	651(47.52%)	305(56.80%)
	≥1	13902(56.26%)	719(52.48%)	232(43.20%)
Smoking during Pregnancy	No	20357(82.38%)	1046(76.35%)	412(76.72%)
	Yes	4354(17.62%)	324(23.65%)	125(23.28%)
Maternal Asthma	No	23648(95.69%)	1284(93.72%)	494(91.99%)
	Yes	1065(4.31%)	86(6.28%)	43(8.01%)
Maternal Age	<21 years	2166(9.01%)	129(9.66%)	51(9.85%)
	21-34 years	18150(75.51%)	970(72.66%)	384(74.13%)
	>34 years	3719(15.47%)	236(17.68%)	83(16.02%)
Pre-Pregnancy Body Mass Index	≤18.5 kg/m^2	7417(30.01%)	385(28.10%)	154(28.68%)
	18.5-24.9 kg/m^2	11724(47.44%)	695(50.73%)	259(48.23%)
	25.0-29.9 kg/m^2	3331(13.48%)	169(12.34%)	60(11.17%)
	>30.0 kg/m^2	2241(9.07%)	121(8.83%)	64(11.92%)
Gestational Diabetes	No	23742(96.07%)	1291(94.23%)	507(94.41%)
	Yes	971(3.93%)	79(5.77%)	30(5.59%)
Preeclampsia	No	24180(97.87%)	1216(88.95%)	427(79.52%)
	Preeclampsia	526(2.13%)	151(11.05%)	110(20.48%)
Placenta Previa	No	24590(99.50%)	1323(96.57%)	512(95.34%)
	Yes	123(0.50%)	47(3.43%)	25(4.66%)
Placental Abruption	No	24461(98.98%)	1280(93.43%)	408(75.98%)
	Yes	252(1.02%)	90(6.57%)	129(24.02%)
Umbilical Cord Complication	No	16979(68.70%)	418(30.51%)	396(73.74%)
	Cord around the neck or body, knot in the cord, prolapsed or lacerated cord	7490(30.31%)	927(67.66%)	129(24.02 %)
	Short, 2-vessel or velamentous cord	244(0.99%)	25(1.82%)	12(2.23%)
Gestational Weight Gain	Normal	22409(90.68%)	1288(94.01%)	521(97.02%)
	<10lb at 30 weeks' or <20 lbs at term	242(0.98%)	20 (1.46%)	6(1.12%)
	>40 lbs at term			

		2062(8.34%)	62(4.53%)	10(1.86%)
Birth Weight Category	SGA	1960(7.95%)	117(8.54%)	66(12.29%)
	AGA	20128(81.65%)	1092(79.71%)	430(80.07%)
	LGA	2564(10.40%)	161(11.75%)	41(7.64%)
Anaemia	No	23777(96.75%)	1293(94.86%)	482(90.09%)
	Yes	798(3.25%)	70(5.14%)	53(9.91%)
Placenta Delivery	Spontaneous	16640(67.98%)	851(62.71%)	245(45.79%)
	Expressed or assisted	2661(10.87%)	105(7.74%)	12(2.24%)
	Manual	5053(20.64%)	385(28.37%)	257(48.04%)
	Retained	125(0.51%)	16(1.18%)	21(3.93%)
Predictor Variables (Continuous)				
Maternal Height *(inches)*		64.78(±2.48)	64.49(±2.42)	64.(±2.49)

Table 5.2: Univariable Analyses Stratified by Gestational Age Categories: Factors Associated with Low and High PWR's

Predictors		Gestational Age ≥37 Weeks'		Gestational Age between 32-37 Weeks'		Gestational Age ≤32 Weeks'	
		Odds Ratio for PWR <10th Percentile (95% Confidence Interval)	Odds Ratio for PWR >90th Percentile (95% Confidence Interval)	Odds Ratio for PWR <10th Percentile (95% Confidence Interval)	Odds Ratio for PWR >90th Percentile (95% Confidence Interval)	Odds Ratio for PWR <10th Percentile (95% Confidence Interval)	Odds Ratio for PWR >90th Percentile (95% Confidence Interval)
Parity	0	-	-	-	-	-	-
	≥1	0.915 (0.832, 1.006)	1.073 (0.979, 1.176)	0.687 (0.435, 1.084)*	1.686 (1.094, 2.598)*	0.604 (0.339, 1.077)*	2.170 (1.128, 4.174)*
Smoking During Pregnancy	No *(ref)*	-	-	-	-	-	-
	Yes	0.647 (0.559, 0.749)*	1.795 (1.616, 1.994)*	0.493 (0.256, 0.947)*	1.518 (0.970, 2.378)	0.938 (0.494, 1.779)	0.630 (0.271, 1.465)
Maternal Asthma	No *(ref)*	-	-	-	-	-	-
	Yes	0.809 (0.642, 1.020)	1.085 (0.890, 1.322)	0.965 (0.405, 2.298)	1.075 (0.500, 2.308)	0.878 (0.331, 2.332)	0.492 (0.114, 2.119)
Maternal Height	*For every 10cm increase*	1.013 (0.993, 1.033)	1.001 (0.982, 1.020)	1.027 (0.933, 1.130)	1.034 (0.946, 1.131)	1.123 (1.004, 1.255)*	1.139 (0.993, 1.306)
Maternal Age	<21 years	0.881 (0.736, 1.055)	1.217 (1.042, 1.421)*	0.265 (0.064, 1.104)	1.206 (0.596, 2.439)	0.679 (0.231, 2.000)	1.148 (0.381, 3.464)
	21-34 years	-	-	-	-	-	-
	>34 years	1.079 (0.949, 1.226)	0.998 (0.877, 1.136)	1.283 (0.744, 2.211)	1.291 (0.767, 2.173)*	0.578 (0.237, 1.410)*	1.139 (0.476, 2.721)
Pre-pregnancy BMI	≤18.5 kg/m^2	0.923 (0.829, 1.027)	1.296 (1.161, 1.446)*	1.018 (0.610, 1.698)	1.494 (0.891, 2.505)	0.569 (0.314, 1.030)	0.898 (0.427, 1.891)
	18.5-24.9 kg/m^2 *(ref)*	-	-	-	-	-	-
	25.0-29.9 kg/m^2	0.827 (0.709, 0.965)*	1.218 (1.050, 1.413)*	0.807 (0.379, 1.718)	1.137 (0.549, 2.357)	0.416 (0.151, 1.144)	0.863 (0.292, 2.555)
	>30.0 kg/m^2	0.805 (0.670, 0.967)*	1.522 (1.296, 1.787)*	0.708 (0.263, 1.902)	2.326 (1.141, 4.744)	0.313 (0.104, 0.942)*	0.814 (0.276, 2.403)
Gestational Diabetes	No *(ref)*	-	-	-	-	-	-
	Yes	0.707	1.513	0.194	1.014	0.475	0.342

		(0.533, 0.937)*	(1.240, 1.846)*	(0.026, 1.422)	(0.424, 2.423)	(0.110, 2.052)	(0.045, 2.583)
Preeclampsia	No *(ref)*	-	-	-	-	-	-
	Preeclampsia	0.979 (0.691, 1.387)	1.775 (1.364, 2.309)*	1.028 (0.479, 2.206	1.834 (1.026, 3.276)*	1.173 (0.615, 2.237)*	1.397 (0.673, 2.902)
Placental Previa	No *(ref)*	-	-	-	-	-	-
	Yes	0.747 (0.344, 1.619)	0.980 (0.507, 1.895)	0.341 (0.046, 2.527)	0.282 (0.038, 2.085)	1.500 (0.415, 5.424)	3.919 (1.324, 11.601)*
Placental Abruption	No *(ref)*	-	-	-	-	-	-
	Yes	1.223 (0.795, 1.881)	2.077 (1.485, 2.903)*	0.523 (0.160, 1.705)	2.268 (1.216, 4.229)*	0.592 (0.290, 1.212)*	1.678 (0.857, 3.285)*
Umbilical Cord Complications	None *(ref)*	-	-	-	-	-	-
	Cord around the neck or body, knot in the cord, prolapsed or lacerated cord	0.810 (0.728, 0.901)*	1.189 (1.080, 1.309)*	0.973 (0.594, 1.592)	1.545 (1.001, 2.386)	0.850 (0.439, 1.646)	0.816 (0.376, 1.774)
	Short, 2-vessel or velamentous cord	1.990 (1.390, 2.850)*	1.180 (0.753, 1.851)	0.771 (0.092, 5.482)	3.622 (1.269, 10.338)*	6.603 (1.835, 23.755)*	3.661 (0.681, 19.674)
Gestational Weight Gain	<10lb at 30 weeks' or <20 lbs at term	0.713 (0.427, 1.190)	1.002 (0.654, 1.537)	0.579 (0.076, 4.398)	∞ (0, ∞)	1.278 (0.147, 11.131)	∞ (0, ∞)
	Normal *(ref)*	-	-	-	-	-	-
	>40 lbs at term	0.821 (0.690, 0.977)	1.014 (0.868, 1.184)	0.474 (0.113, 1.993)	1.646 (0.752, 3.605)	0.799 (0.098, 6.502)	1.149 (0.140, 9.421)
Birth Weight Category	SGA	1.130 (0.952, 1.342)	1.242 (1.057, 1.461)*	1.444 (0.689, 3.026)	1.322 (0.654, 2.669)	0.691 (0.262, 1.822)	1.708 (0.742, 3.929)
	AGA *(ref)*	-	-	-	-	-	-
	LGA	0.829 (0.701, 0.981)*	1.096 (0.946, 1.270)	1.419 (0.738, 2.728)	1.462 (0.808, 2.647)	1.110 (0.410, 3.006)	0.343 (0.045, 2.603)
Anaemia		-	-	-	-	-	-

	No *(ref)*						
	Yes	0.767 (0.560, 1.052)	1.898 (1.538, 2.342)*	0.799 (0.242, 2.643)	2.420 (1.170, 5.008)*	0.849 (0.320, 2.253)	2.677 (1.187, 6.037)*
Placental Delivery	Spontaneous *(ref)*	-	-	-	-	-	-
	Expressed or assisted	1.186 (1.006, 1.397)*	0.915 (0.771, 1.086)	1.131 (0.432, 2.963)	1.393 (0.604, 3.212)	1.144 (0.129, 10.114)	0 $(0, \infty)$
	Manual	1.108 (0.987, 1.244)*	1.010 (0.903, 1.130)	1.054 (0.630, 1.762)	1.329 (0.845, 2.090)	0.659 (0.369, 1.176)	2.156 (1.060, 4.383)*
	Retained	3.832 (2.344, 6.264)*	1.450 (0.737, 2.854)*	5.657 (1.374, 23.290)*	1.658 (0.196, 14.010)	3.119 (1.077, 9.033)*	4.159 (1.022, 16.931)*

*-Covariates with a significance level of $p<0.05$

Table 5.3: Final Multivariable Logistic Regression model of Baseline Pregnancy Factors Hypothesized to Influence a Placental Weight Ratio either ≤10th or ≥90th percentile by Gestational Age Category

	Odds Ratio (95% Confidence Interval)					
	Gestational Age ≥37 Weeks'		**Gestational Age between 32 and 37 Weeks'**		**Gestational Age ≤32 Weeks'**	
Predictors	**PWR <10th Percentile**	**PWR >90th Percentile**	**PWR <10th Percentile**	**PWR >90th Percentile**	**PWR <10th Percentile**	**PWR >90th Percentile**
Parity						
0	-	-	-	-	-	-
≥1	0.928 (0.841, 1.024)*	1.067 (0.969, 1.176)*	0.661 (0.412, 1.059)*	1.612 (1.011, 2.570)**	0.576 (0.306, 1.084)*	2.224 (1.060, 4.664)**
Smoking During Pregnancy						
No *(ref)*	-	-	-	-	X	X
Yes	0.609 (0.522, 0.711)**	1.808 (1.618, 2.019)**	0.542 (0.278, 1.055)*	1.583 (0.987, 2.540)**		
Maternal Age						
<21 years 21-34 years >34 years	X	X	X	X	X	X
Maternal Height *For every 10cm increase*	X	X	X	X	1.131 (1.005, 1.272)**	1.139 (0.984, 1.318)*
Pre-pregnancy BMI						
≤18.5 kg/m^2	0.907 (0.811, 1.014)*	1.263 (1.126, 1.417)**	X	X	X	X
18.5-24.9 kg/m^2 *(ref)*	-	-				
25.0-29.9 kg/m^2	0.813 (0.694, 0.953)**	1.223 (1.050, 1.426)**				
>30.0 kg/m^2	0.806 (0.666, 0.975)**	1.402 (1.184, 1.661)**				
Gestational Diabetes			X	X	X	X
No *(ref)*	-	-				

Gestational Diabetes	0.734 (0.551, 0.979)**	1.442 (1.176, 1.770)**				
Preeclampsia						
No *(ref)*	X	-	X	-	X	X
Preeclampsia		1.684 (1.281, 2.213)**		1.938 (1.040, 3.610)**		
Placental Previa						
No *(ref)*	X	X	X	X	X	-
Yes						3.333 (0.904, 12.285)**
Placental Abruption						
No *(ref)*	X	-	X	-	X	X
Yes		2.084 (1.481, 2.931)**		1.991 (1.027, 3.861)**		
Umbilical Cord Complications						
None *(ref)*	-	-		-	-	
Cord around the neck or body, knot in the cord, prolapsed or lacerated cord	0.821 (0.735, 0.916)**	1.183 (1.071, 1.308)**	X	1.453 (0.918, 2.298)*	X	X
Short, 2-vessel or velamentous cord	1.932 (1.338, 2.790)**	X		3.745 (1.240, 11.307)**	5.298 (1.395, 20.128)*	
Birth Weight Category						
SGA	1.153 (0.963, 1.381)*	1.109 (0.934, 1.317)*				
AGA *(ref)*	-	-	X	X	X	X
LGA	0.824 (0.693, 0.980)**	1.114 (0.955, 1.298)*				
Anaemia						
No *(ref)*	X	-	X	-	X	X
Yes		1.876		2.068		

		(1.507, 2.336)**		(0.961, 4.448)*		
Placental Delivery Spontaneous *(ref)*	-				-	
Expressed or assisted	1.163 (0.976, 1.387)*	X	X	X	X	X
Manual	1.104 (0.981, 1.243)*				0.616 (0.324, 1.174)*	
Retained	4.053 (2.461, 6.675)**				3.452 (1.095, 10.881)**	

*-Covariates with a significance level of p<0.20; **-Covariates with a significance level of p<0.05; Factors considered but not significant in any of the models were maternal asthma and gestational weight gain

CHAPTER 6: INTEGRATED DISCUSSION

This chapter summarizes the thesis results and implications, provides a detailed discussion where appropriate, identifies limitations and strength and provides recommendations for future research. While multiple objectives were addressed, the main purpose of this thesis was twofold: to established norms for the placental weight ratio (PWR) across gestational age, and compare these norms between small, average and large for gestational age infants (SGA, AGA and LGA) and to use the PWR norms we established to identify risk factors associated with atypical PWRs in different gestational age categories.

6.1 Brief Summary of Results

6.1.1 Population-Based Placental Weight Ratio Distributions

The placental and birth weight distributions show that placental growth has to some degree levelled off while fetal growth continues at an accelerated pace. This pattern is reflective of the second half of gestation. Comparing the city-wide population to the total sample PWR distributions revealed them to be similar, with small differences presenting themselves at the extreme percentiles at the earlier gestational ages. In general, the females have higher PWR's than males. These PWR distribution curves make a substantial contribution to the literature. They show how the PWR changes across gestation by percentile.

The curves that are stratified by fetal growth adequacy are the first of their kind. Distinctly, they show that SGA infants had much higher PWR's in early gestation than both LGA and AGA infants at the early gestations. On the other hand, LGA infants have lower PWR's at the lower gestational ages when compared to AGA infants. However, the PWR's at term gestations are nearly identical in both SGA and LGA infants. In fact, LGA infants have slightly higher median ratios at term than both SGA and AGA infants.

6.1.2 Determinants of Atypical Placental Weight Ratios

The results presented in Chapter 5 suggest that adverse obstetric conditions are associated with either placental growth restriction or placental hypertrophy, or both, based on gestational age at birth. Inferences are sharpened by the use of PWR, rather than merely placental weight, since PWR presents an opportunity to look at placental growth in relation to birth weight.

For infants born at ≥37 weeks gestation, factors associated with an increased risk of PWR<10^{th} percentile were: a short, 2-vessel or velamentous umbilical cord insertion, SGA infants, and any assisted placental delivery methods. On the other hand, multiparity, smoking, abnormal BMI, preeclampsia, placental abruption, a cord around the neck or body, a knot in the cord, or a prolapsed or lacerated cord, both SGA and LGA infants and maternal anaemia increased the odds of a PWR>90^{th} percentile.

For infants born between 32 and 37 weeks gestation, multiparity and smoking attenuated the odds of a PWR<10^{th} percentile. Alternatively, multiparity, preeclampsia, placental abruption, a cord around the neck or body, a knot in the cord, or a prolapsed or lacerated cord, a short, 2-vessel or velamentous umbilical cord insertion, and maternal anaemia all increased the odds of a PWR >90^{th} percentile.

For infants born ≤32 weeks gestation, increasing maternal height and a short, 2-vessel or velamentous umbilical cord insertion increased the odds of a PWR <10^{th} percentile. Multiparity, increasing maternal height and placental previa all increased the odds of a PWR >90^{th} percentile.

The majority of the risk factors considered resulted in increased odds of a PWR ≥90^{th} percentile. This proposes that the placenta may have compensatory responses to maternal obstetric conditions, potentially each with a distinct pathophysiologic mechanism, but similar PWR outcome.

6.1.3 Integration of Findings

Collectively, the results from this thesis supplement the literature on the PWR by first creating population standards and comparing the standards between SGA, AGA and LGA infants. Subsequently, we examined various risk factors proposed to be associated

with atypical placental and fetal growth using the standards we created. The results of the distributions allowed us to use gestational age and sex specific population-based standards to identify infants as having a PWR<10th percentile or >90th percentile. Furthermore, it afforded us the opportunity to examine multiple maternal obstetric conditions and baseline factors that might influence the PWR using large scale population standards.

6.2 Detailed Discussion of Determinants of Placental Weight Ratios

The framing of the findings in the context of hypoxia of various mechanisms is a useful framework in which to interpret the findings of Chapter 5. The following section presents a more detailed discussion which expands on points introduced in Chapter 5.

Ischemic Placental Disease

Ischemic placenta disease (IPD), which describes fetal growth restriction, placental abruption and preeclampsia have been shown to apply its effects differently in term and preterm infants.[1,2] Among infants with IPD, the frequency of SGA is higher in term, than preterm, infants.[1] Interestingly, SGA was only significantly associated with atypical PWRs in term infants after controlling for other factors in our analyses. Furthermore, when PWRs have been compared between AGA and SGA infants based on gestational age, SGA infants are found to have higher ratios than AGA infants.[3] Our results agree with both of these separate, yet dependant observations, and provide further evidence that the role of the placenta in relation to fetal weight differs between complications and timing during pregnancy.

Ananth et al.[1] have shown that IPD in preterm infants is more likely to include the mother and the fetus through SGA, preeclampsia and placental abruption, than in term infants. A common pathophysiology between preeclampsia and placental abruption is indicated by the sharing of a large proportion of risk factors.[4] Our results have shown that preeclampsia and placental abruption increase the odds of a PWR ≥90th percentile in the highest two gestational age categories. Furthermore, the effect of placental abruption and

preeclampsia in infants born between 32 and 37 weeks on a PWR ≥90th percentile is slightly increased compared to term infants.

Preplacental Hypoxia

Preplacental hypoxia, a reduction in maternal blood oxygen content, occurs when the placenta and fetus become hypoxic due to conditions such as maternal asthma and maternal anaemia.[5] Correlations between mild to severe anaemia and heavier than average placentas have been noted in numerous studies.[6–11] These studies have also shown that hypoxia resulted in a smaller fetus, and therefore the PWR increased.[6–11] For term infants, maternal anaemia was associated with amplified odds of having a PWR≥90th percentile. Our results are in agreement with the proposed physiological mechanism. The increased size of the placenta has been understood as a compensatory mechanism to overcome the lack of oxygen in the maternal blood, as well as the increased trophoblastic proliferation and placental angiogenesis that result from anaemia.[12] In response to a lack of oxygen, the extravillous trophoblast of the placenta bed shows an increased depth of invasion and the villi appear hypercapillarized.[13]

Uteroplacental Hypoxia

Uteroplacental hypoxia occurs when normally oxygenated maternal blood has restricted entry into the uteroplacental tissues due to either occlusion or failed trophoblast invasion of the uteroplacental arterioles. This situation represents late onset growth restriction with preserved end diastolic flow volume, and term preeclampsia.[5] Both low and high placental weight has been shown in the literature to be associated with term preeclampsia.[14] Our results indicate that individuals with preeclampsia who deliver an infant at term have increased odds of a PWR ≥90th percentile. These results are congruent with current literature which shows that the PWR is often increased in pregnancies that are complicated by preeclampsia.[15,16] This suggests that there is compensatory growth of placental villi in an attempt to overcome an unfavourable maternal environment.[17,18]

Our results do not show increased odds for having a PWR $\leq 10^{th}$ percentile, thereby indicating a potentially smaller placenta. However, since we do not have the timing of diagnosis for preeclampsia, we were only looking at infants born at term whose mothers had preeclampsia. Nevertheless, the majority of pregnancies with preterm preeclampsia do result in a preterm delivery.[19]

Postplacental Hypoxia

Postplacental hypoxia is when oxygenated maternal blood enters the intervillous space at a normal or reduced rate, but a defect in fetoplacental perfusion prevents the fetus from receiving sufficient oxygen.[5] Placental adaptations in mothers with pre-gestational diabetes resemble those adaptations seen in other postplacental hypoxia conditions. Placentas from women with gestational diabetes are often increased in weight when compared to women who had only one abnormal oral glucose tolerance test.[20–25] However, the literature is inconclusive on the effect of gestational diabetes on the PWR.[21,26]

In our highest gestational age categories, gestational diabetes was associated with increased odds of a PWR $\geq 90^{th}$ and was protective against a PWR $\leq 10^{th}$ percentile. Levels of haemoglobin and erythropoietin provide evidence that fetuses in mothers with pre-diabetes are hypoxic. The literature suggests that the surface and exchange areas are enlarged as a result of the hypoproliferation and hypervascularization in gestational diabetes. Therefore, the maternal placental oxygen supply is reduced, and the fetal oxygen demand is increased.[27,28] This phenomenon could be explained by aerobic metabolism which is stimulated by fetal hypersinsulinemia which can result in reduced trophoblast proliferation. The low oxygen levels up regulate transcriptional synthesis of leptin, VEGF and fibroblast growth factor which promotes placental endothelial cell proliferation. The result is enhanced vascularisation of the placenta.[29,30]

Carbon Monoxide Hypoxia

Maternal smoking is associated with carbon monoxide hypoxia which reduces oxygen content in maternal blood. While this seems similar to preplacental hypoxia, and the changes in fetal capillaries and peripheral villi do mirror the effects in cases such as anaemia, the morphology and oxygen diffusion conductances are not consistent with other cases of preplacental hypoxia.[31,32] However, these differences may be confounded by some of the other toxins in cigarettes.[33]

Cigarette smoking is associated with a decreased fetal weight, but of the few studies that have examined the association between maternal smoking and placental weight, there has been no significant effect found.[9,34–38] Some studies that investigated the PWR found significantly higher ratios in smokers versus non-smokers.[36,39] On the other hand, another study found a significantly lower PWR for smokers than non-smokers.[34] Our results account for such discrepancies as we found that smoking increases the odds of having a PWR $\geq 90^{th}$ percentile and attenuates the odds of having a PWR $\leq 10^{th}$ percentile. When a mother smokes during pregnancy, the placenta and fetus become hypoxic because of a reduction of oxygen content within the maternal blood along with an increased vascular resistance on the fetal side of the placenta. These conditions result in reduced intraplacental oxygen content, predominately branching angiogenesis and reduced vascular impedance. The increase in branching angiogenesis, and thereby reduced vascular impedance, is an adaptive mechanism to the hypoxic state. This mechanism is associated with excessive placental weight.[40]

Placental and Umbilical Cord Complications

Placentas with a non-centrally inserted umbilical cord, such as a velamentous insertion, tend to be heavier.[41] Any force that compresses umbilical cords may lead to diminished blood flow in umbilical vessels and subsequent fetal hypoxia or circulatory compromise. Mechanical cord compression can be caused by cord entanglements (nuchal/body cords) and cord prolapse; or it may take place as a result of an abnormal configuration of the cord such as true knots, hypercoiling, abnormally short or long cords, abnormal cord insertions, or strictures.[42] These complications are often associated with decreased fetal weight, and both marginal and velamentous cord insertion are associated

with an decreased placental weight, an increased PWR and a reduced metabolic efficiency.[3,41,43] On the contrary, a single umbilical artery is also associated with a reduced placental weight.[43] Abnormal cord insertion has also been found to be associated with a high PWR.[44] Our results show that a short, 2-vessel or velamentous cord insertion are associated with increased odds of a PWR $\geq 90^{th}$ percentile in infants born between 32 and 37 weeks, and increased odds of a PWR $\leq 10^{th}$ percentile in terms infants and infants born $\leq$32 weeks. However, a cord around the neck or body, knot in the cord, prolapsed or lacerated cord is also associated with a PWR $\geq 90^{th}$ percentile in all infants born at >32 weeks.

As indicated within the literature, some placental factors, such as placenta abruption, placenta previa and antepartum hemorrhage are not individually associated with placental weight,[43] but as a group are associated with a decreased PWR.[45] Our results partially disagree with these findings. We found that placenta previa has no significant association, but that placental abruption strengthened the odds of having a PWR $\geq 90^{th}$ percentile.

6.3 Study Implications

Findings from this thesis have potentially important implications for implementing the population based PWR standards in research.

6.3.1 Applications of the Placental Weight Ratio Distributions in Research

Future research directions can make use of the PWR distributions for identifying infants with atypical PWRs. Previous studies that have looked at atypical PWRs have not used a population standard to identify abnormal PWRs.[15–17] Furthermore, the SGA, AGA and LGA distribution curves can provide new dimension in future similar studies.

6.4 Strengths and Limitations

A major strength of the study is the available sample size. The perinatal database provided a large number of observations with a placental weight, birth weight and gestational age. This allowed for the creation of accurate standards. It also allowed for the percentile curves to be stratified by fetal growth adequacy which required large enough sample sizes in each of the fetal growth adequacy categories. This study is strong due to the quality and comprehensive nature of the data. The internal validity of the study is strong because every birth at St. Joseph's Hospital and Victoria Hospital was captured; this is a population-based, representative sample. The results will be important for both obstetricians and neonatologists managing high risk pregnancies and infants with extreme birth and placental weights.

This research is novel in the approach of considering a modern framework of proposed physiological mechanisms along with a theoretic framework to examine the relationships between various risk factors and their associations with atypical PWRs. The strong theoretical framework, based on biologically plausible mechanistic literature, combined with epidemiological literature provides a strong base for this study. This approach also allows the complexity of the relationships that exist between factors to be conserved and provides an understanding of how these factors relate within this population.

The appropriate use of quantile regression (QR) is a principle strength of the study since it does not make any distributional assumption beforehand. It is able to model data with heterogeneous conditional distributions, and it is robust to extreme values of the outcome. Furthermore, compared to other statistical methods QR is more stable and is able to reveal departures from underlying assumption of parametric models.[50]

Like other studies that use administrative databases, this study was unable to assess a few covariates that may influence the PWR. Examples include residing at high altitude and ethnicity. However, residing at high altitude, a form of preplacental hypoxia, is not a variable of great significance for many women living in the region. Preplacental

hypoxia was represented by other variables in the study. Ethnicity has been shown to influence the PWR in previous studies, but the effect was small.[9,53]

Height and weight data contributing to the calculation for pre-pregnancy came from variable sources, including self-report, therefore misreporting may have influenced the accuracy of BMI. We speculate it may have produced an underestimate in BMI. The situation is similar for smoking because women sometimes fail to report such behaviours. Generally, because these are secondary data from an administrative data source, we cannot be certain as to how error-free the data are. We have excluded implausible values as an effort to control the data quality.

6.5 Future Directions

Further studies are warranted to provide comparisons in other populations. Birth weights are known to vary from country to country.[52,54] Therefore, the creation of PWR distribution curves in other populations is recommended, as percentiles can best be used as a standard in research studies if they can be argued to be comparable to the population in which the studies are conducted.

Our data are cross-sectional. This is typical of studies which establish growth standards based on birth outcomes.[52] However, neonates at early gestations are likely not representative of their same-gestation peers who remain in utero. It would be of interest to conduct longitudinal studies looking at serial estimates of placental and fetal growth in order to further understand the timelines attached to growth deviations. Longitudinal studies following a cohort of placentas throughout the pregnancy would require serial ultrasound estimation; however, ultrasound weight estimations have their inaccuracies.[51]

Further research is justified to elucidate the biological mechanisms underlying the associations between anemia, gestational diabetes, hypertensive disease, maternal pre-pregnancy BMI, and umbilical cord complications with abnormal placental growth relative to fetal growth. Additionally, understanding the biological mechanisms in infants

at different gestational ages is vindicated based on the differing results seen in the three gestational age categories we examined for risk factors such as preeclampsia and placental previa.

Additionally, future cohort studies should examine these associations to determine if children with either low or high PWRs are at a greater risk for certain medical conditions. Limited literature exists that examines later child health outcomes in infants with atypical PWRs.

All of the aforementioned prospective directions can make use of the PWR standards we created, as they provide a large population-based standard to define atypical PWRs in across the second half of pregnancy. Furthermore, the stratified curves may provide a new dimension in future studies.

6.6 Conclusions

The PWR distribution curves make a substantial contribution to the literature. They show how the PWR changes across gestation by percentile. Further, the PWR distribution curves provide a standard that clinicians and researchers can apply as a reference standard to identify infants who have abnormal PWRs. Identifying infants with high PWRs is important for patient care in both the short and long term. Previous literature has shown that neonates with a high PWR had increased incidence of short-term complications.[55] Furthermore, in recent years, birthweight, sometimes in conjunction with placental weight, has been associated with the development of a series of diseases later in life.[56] However, the relative magnitude of the PWR, in terms of standards, is not available for all gestational ages in a Canadian population. As well, PWR has not been documented for SGA, AGA and LGA infants. Thus, the distributions estimated in this study may provide a useful tool for adding this dimension in future similar studies.

Using the population-based standards we created to define the PWR we found that both maternal obstetric conditions and maternal baseline factors are either associated with

placental growth restriction or placental hypertrophy in relation to birth weight, and even both, based on gestational age at delivery. The majority of the risk factors assessed resulted in increased odds of a PWR $\geq 90^{th}$ percentile. This suggests that the placenta may have particular compensatory responses to maternal obstetric conditions, each with a different pathophysiologic mechanism, but comparable PWR outcome.

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APPENDICES

Appendix A: Definitions

Asymmetrical Small for Gestational Age- an infant with a ponderal index less than the 10^{th} percentile, based on population standards for each sex by gestational age.

Average for Gestational Age- an infant with a birth weight between the 10^{th} and 90^{th} percentile after controlling for gestational age and sex, as defined by the World Health Organization in the International Classification of Diseases Version 10, as per code P05.1.

Blastocyst- a structure formed in the early embryogenesis of mammals, after the formation of the morula. It contains an inner cell mass which eventually forms the fetus, and the outer cell mass containing trophoblasts which later forms the placenta.

Body Mass Index- the individuals weight in kilograms divided by their height in meters squared.

Decidua- is the uterine lining which forms the maternal part of the placenta.

Extravillous Trophoblasts- cells which originate from the trophoblasts. Extravillous trophoblast grow out from the placenta and penetrate into the decidualised uterus. This process attaches the placenta to the mother, and alters the vasculature in the uterus to allow it to provide an adequate blood supply to the growing fetus as pregnancy progresses.

Fetal Growth Restriction- a fetus that has not reached its growth potential because of genetic or environmental factors.

Lacunae- one of the blood spaces of the placenta in which the fetal villi are found.

Large for Gestational Age- an infant who exceed the 90^{th} percentile for birth weight after controlling for gestational age and sex, as defined by the World Health Organization in the International Classification of Diseases Version 10, as per code P05.1.

Morula- an embryo at an early stage of embryonic development, consisting of a ball of about 16 undifferentiated cells contained inside the zona pellucida.

Placental Weight Ratio- the ratio of the placental weight in grams to the fetal weight in grams.

Ponderal Index- the birth weight in kilograms divided by the length in meters cubed, according to Rohrer(1908).

Preeclampsia- is a conditional that occurs when a pregnant woman develops high blood pressure (>140/90mmHg) and protein in the urine after the 20^{th} week of pregnancy.

Small for Gestational Age- an infant that weighs less than the 10^{th} percentile for their gestational age and sex, as defined by the World Health Organization in the International Classification of Diseases Version 10, as per code P05.1

Symmetrical Small for Gestational Age- an infant with a ponderal index greater than the 10^{th} percentile, based on population standards for each sex by gestational age.

Syncytiotrophoblast- the thick layer of cell boundary that forms the endometrial stroma. It secretes human chorionic growth hormone in order to maintain progesterone secretion and sustain pregnancy. It is a specialized epithelium covering the villous tree and has several functions, such as transport of gases, nutrients, and waste products and synthesis of peptide and steroid hormones that regulate placental, fetal, and maternal systems

Trophoblasts- cells forming the outer layer of the blastocyst.

Appendix B: Research Ethics Board Approval

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Karen Campbell
Review Number: 17999E
Review Level: Delegated
Approved Local Adult Participants: 40000
Approved Local Minor Participants: 0
Protocol Title: Standardized statistical curves of fetal growth symmetry
Department & Institution: Epidemiology & Biostatistics, University of Western Ontario
Sponsor:
Ethics Approval Date: July 29, 2011 **Expiry Date:** March 31, 2016
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
UWO Protocol		

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

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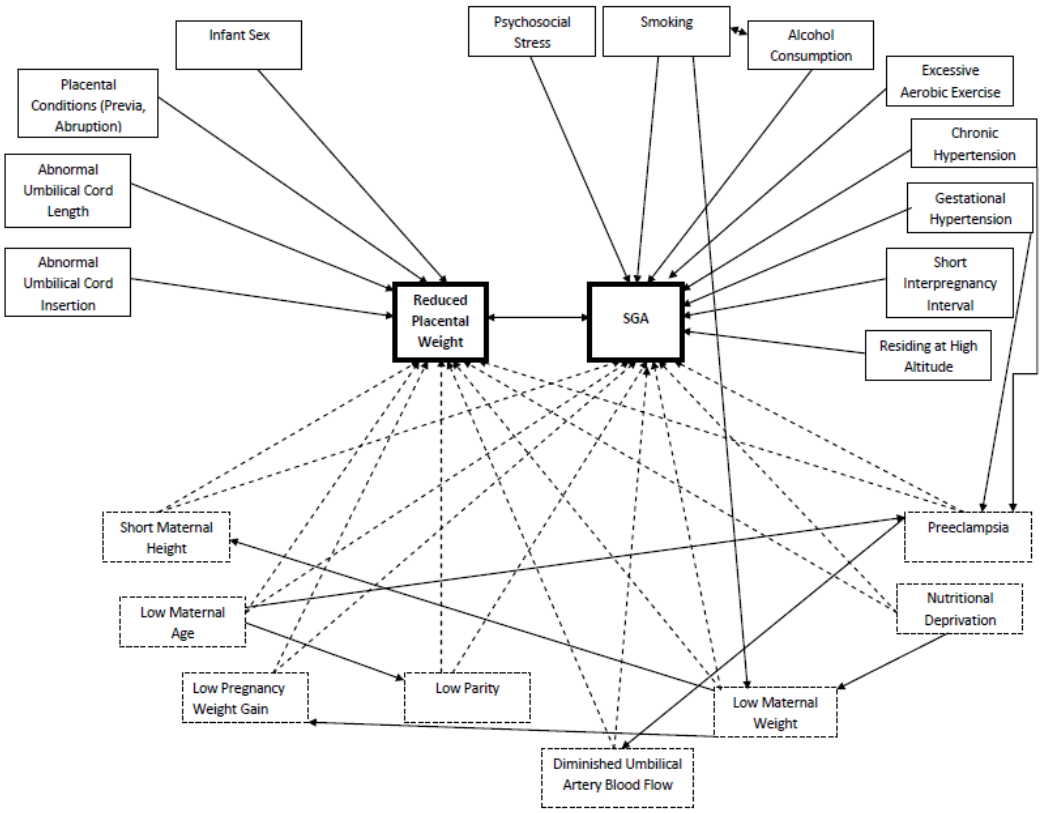
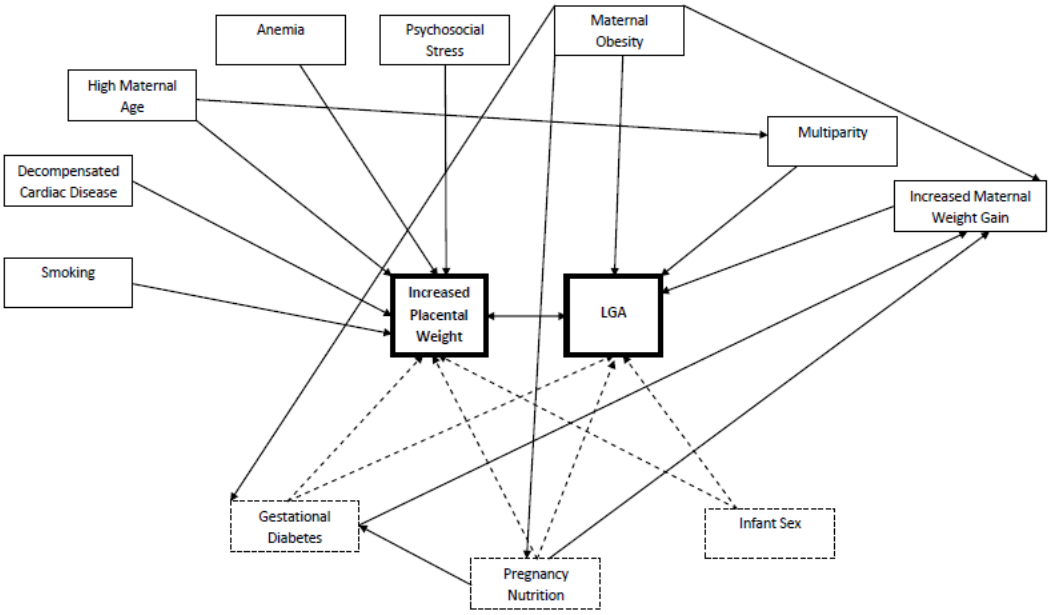
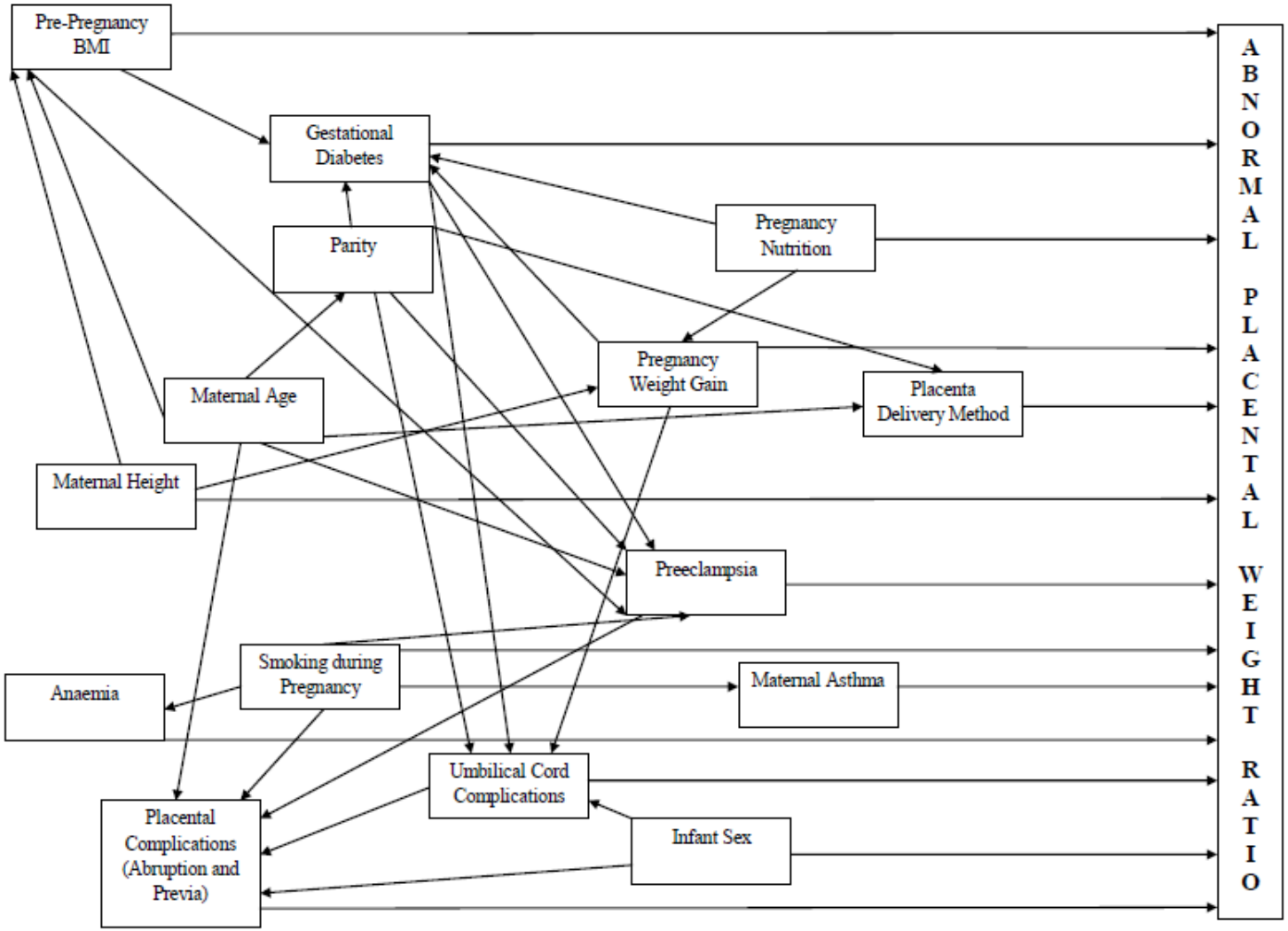
Appendix C: Conceptual Model of Risk Factors Associated with Reduced Placental Weight and SGA



Appendix D: Conceptual Model of Risk Factors Associated with Increased Placental Weight and LGA



Appendix E: Conceptual Model of the Risk Factors Association with an Atypical PWR



Appendix F: Tables of References for Risk Factors Associated with SGA, LGA and both Reduced and Increased Placental Weights

Risk Factors	References for SGA	References for Reduced Placental Weight	References for LGA	References for Increased Placental Weight
Short Maternal Height	(Xun et al., 2007)(M. S. Kramer, 1987)(Voigt et al., 2010)	(L. A. Williams et al., 1997)		
Low Maternal Weight	(Reader, 2007)(Voigt et al., 2010)(Hibbert et al., 1999)	(Thame et al., 2001)(Junichi Hasegawa et al.,2011)(Hibbert et al., 1999)(Naeye, 1987) (L. A. Williams et al., 1997)(Baptiste-Roberts et al., 2008)		
Low Pregnancy Weight Gain	(Reader, 2007)(Berghella, 2007)(Mamun et al., 2011)(Hellerstedt et al., 1997) (Siega-Riz et al., 2009)(Crane et al., 2009)(Margerison Zilko et al., 2010)	(L. A. Williams et al., 1997)(Naeye, 1987)		
Low Parity	(X. Zhang et al., 2007)	(L. A. Williams et al., 1997)(Baptiste-Roberts et al., 2008)		
High levels of Psychosocial Stress	(Wadhwa et al., 2004)(Goland et al., 1993)(Gracka-Tomaszewska, 2010) (Rondó et al., 2003) (Adams, Eberhard-Gran, Hofoss, & Eskild, 2011) (Chrousos & Gold, 1992)			(Tegethoff, Greene, Olsen, Meyer, & Meinlschmidt, 2010).
Smoking	(M. S. Kramer, 1987)(Romo et al., 2009)(Figueras et al., 2008)(Rasmussen & Irgens, 2006) (Hellerstedt et al.,	(R. E. Christianson, 1979; H. C. Miller, Hassanein, & Hensleigh, 1976; Mochizuki, Maruo, Masuko, & Ohtsu, 1984;		(Pfarrer et al., 1999) (R. E. Christianson, 1979; H. C. Miller, Hassanein, & Hensleigh, 1976; Mochizuki, Maruo,

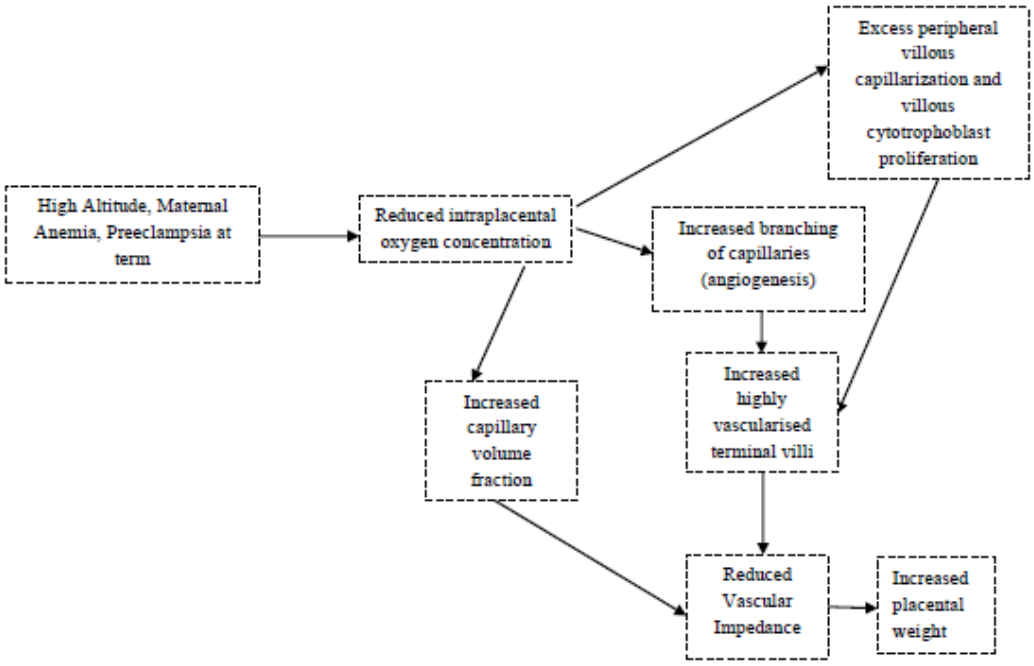
	1997)(Aagaard-Tillery et al., 2008) (Lieberman et al., 1994)(Spinillo et al., 1994)(Aliyu et al., 2010)(Martin & Bracken, 1986) (C. Ward, Lewis, & Coleman, 2007a)(C. Ward, Lewis, & Coleman, 2007b) (Ira M Bernstein et al., 2005)(Berghella, 2007)(Lesley M E McCowan et al., 2009) (Polakowski, Akinbami, & Mendola, 2009) (Lieberman et al., 1994)(Prabhu et al., 2010)	Carolyn M. Salafia, Vintzileos, Lerer, & Silberman, 1992; Wingerd, Christianson, Lovitt, & Schoen, 1976)(Baptiste-Roberts et al., 2008)		Masuko, & Ohtsu, 1984; Carolyn M. Salafia, Vintzileos, Lerer, & Silberman, 1992; Wingerd, Christianson, Lovitt, & Schoen, 1976)(Baptiste-Roberts et al., 2008)
Alcohol Consumption during Pregnancy	(Patra et al., 2011) (Romo et al., 2009) (C. M. O'Leary et al., 2009)			
Excessive Aerobic Exercise during Pregnancy	(M. K. Campbell & Mottola, 2001) (Hopkins et al., 2010) (Lesley M E McCowan et al., 2009) (Erkkola et al., 1992)			
Chronic Hypertension	(Lawrence, 2006) (Catov et al., 2008)			
Gestational Hypertension	(Buchbinder, Sibai, Caritis, Macpherson, Hauth, Lindheimer, Klebanoff, Vandorsten, Landon, Paul, Miodovnik, Meis, & Thurnau, 2002b)(J. C. Hauth et al., 2000)(José Villar et al., 2006) (Buchbinder, Sibai, Caritis, Macpherson, Hauth, Lindheimer, Klebanoff, Vandorsten, Landon, Paul,			

	Miodovnik, Meis, & Thurnau, 2002a)(Baha M Sibai, 2003)			
Preeclampsia	(Eskenazi et al., 1993)(Saftlas, Beydoun, & Triche, 2005)(Rasmussen & Irgens, 2003)(Long et al., 1980)(M. P. Moore & Redman, 1983) (MacKay, Berg, & Atrash, 2001)(X Xiong & Fraser, 2004) (Lars J Vatten & Skjaerven, 2004) (Odegard et al., 2000) (Xu Xiong et al., 2002)	(J Hasegawa et al., 2010)(A Eskild et al., 2009) (A Eskild & Vatten, 2010)(Baptiste-Roberts et al., 2008)(Leung et al., 2001)		(Thomson et al., 1969) (Soma et al., 1982)(P. A. Boyd et al., 1986)(P. M. Coan et al., 2010)(Dahlstrøm et al., 2008)
Nutritional Deprivation	(PW Nathanielsz, 2000)(Nørgård et al., 1999) (R. L. Bergmann et al., 2008)	(Lumey, 1998)(J. M. Wallace, Aitken, Milne, & Hay, 2004a) Heasman, Clarke, Stephenson, & Symonds, 1999) (L. J. Edwards & McMillen, 2001) (Dandrea et al., 2001)(C. Steyn et al., 2001)		
Low and High Maternal Age	(Aldous & Edmonson, 1993) (Strobino et al., 1995)	(Haavaldsen et al., 2011)		
Short Interpregnancy Interval	(van Eijsden et al., 2008). (Conde-Agudelo et al., 2006)			
Toxins	(P. S. Bernstein & Divon, 1997)(Shi Wu Wen et al., 2008)			
Residing at High Altitude	(H L Galan et al., 2001)(L. G. Moore et al., 2001) (Mortola et al., 2000) (Kametas et al., 2004)			(J. Kingdom, Huppertz, Seaward, & Kaufmann, 2000a)
Abnormal umbilical cord insertion		(Junichi Hasegawa et al., 2011) (S Heinonen et al., 2001)		

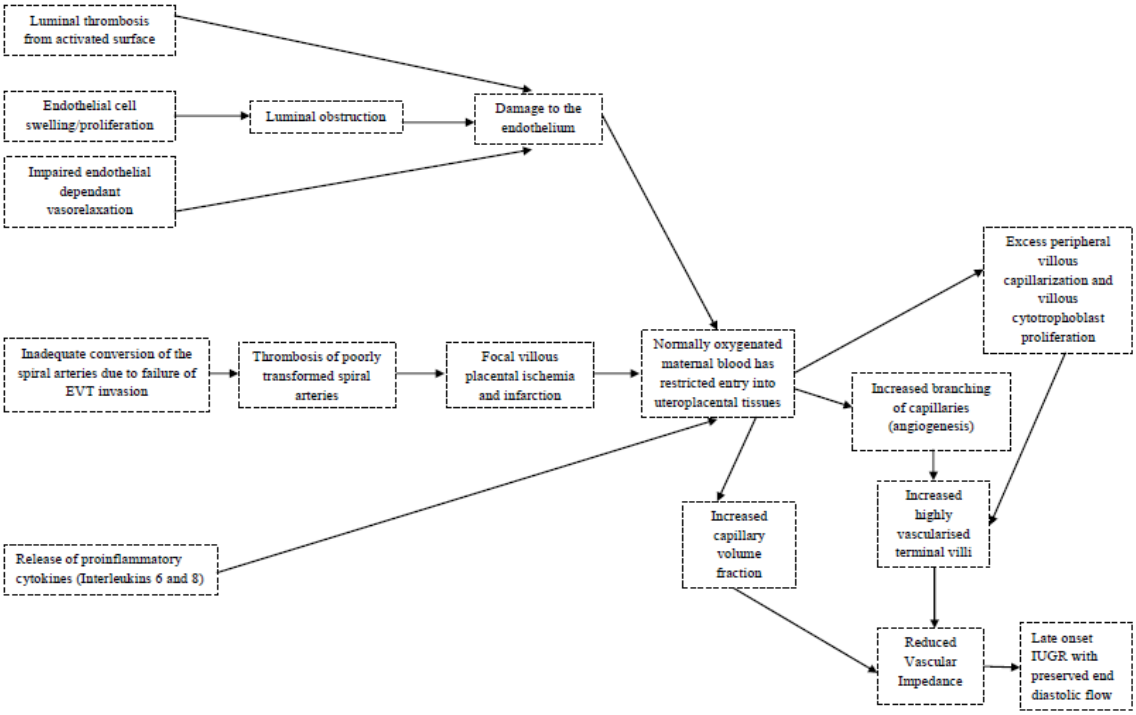
Abnormal cord length		(Junichi Hasegawa et al., 2011)		
Abnormal or Absent Umbilical artery		(Junichi Hasegawa et al., 2011)		
Placental Conditions (Previa, Abruption, Hemorrhage)		(Little et al., 2003)		
Infant Sex (Female)		(S Heinonen et al., 2001) (Naeye, 1987)		
Anemia		(Steer, 1992) (Godfrey et al., 1991)		(Agboola, 1975) (Akhter et al., 2010) (Baptiste-Roberts et al., 2008)(Lao & Wong, 1997)(Lao & Tam, 2000) (Levario-Carrillo et al., 2003)
Ethnicity (African American and Asian)		(Baptiste-Roberts et al., 2008) (Perry et al., 1995)		
Gestational Diabetes			(Langer et al., 2005) (Rodrigues et al., 2000) (Casey et al., 1997) (Hardy, 1999)(Di Cianni et al., 2003) (Stephens et al., 2001) (P. Thureen et al., 2006) (Rosenn, 2008)	(Makhseed et al., 2004) (Kucuk & Doymaz, 2009)(Taricco, Radaelli, Nobile de Santis, & Cetin, 2003b) (Desoye & Hauguel-de Mouzon, 2007)(Johnston, 1995)(Ericsson et al., 2007)(Makhseed et al., 2004)(Kucuk & Doymaz, 2009).
Diabetes Mellitus				(Thomson et al., 1969) (Nummi, 1972)(Clarson et al., 1989)
High Maternal Weight (Obesity)			(Baeten et al., 2001) (Rosenberg et al., 2003)(Cnattingius et al., 1998)(Langer et al., 2005)	(L. A. Williams et al., 1997)(Baptiste-Roberts et al., 2008)
Increased Maternal Weight Gain			(Kahn & Flier, 2000) (Rodriguez et al.,	(Baptiste-Roberts et al., 2008)(L. A. Williams et al.,

			1999)(Okun et al., 1997)(Reader, 2007)	1997)
Multiparity			(Brunskill et al., 1991). (J. A. O'Leary & Leonetti, 1990)	(L. A. Williams et al., 1997)**(**Baptiste-Roberts et al., 2008)
Infant Sex (Male)			(Brunskill et al., 1991) (Lackman, Capewell, Richardson, et al., 2001)	(S Heinonen et al., 2001)(Naeye, 1987)
Pregnancy Nutrition		(L. J. Edwards & McMillen, 2001) (Dandrea et al., 2001)(C. Steyn et al., 2001)	(Denguezli et al., 2009)(Lumey, 1998)	(L. J. Edwards & McMillen, 2001) (Dandrea et al., 2001)(C. Steyn et al., 2001)(Woodall et al., 1996) (Lumey, 1998)
High Maternal Age				(Haavaldsen et al., 2011)
Decompensated Cardiac Disease				(Clavero & Botellallusia, 1963)
High Levels of Psychosocial Stress				(Tegethoff et al., 2010)

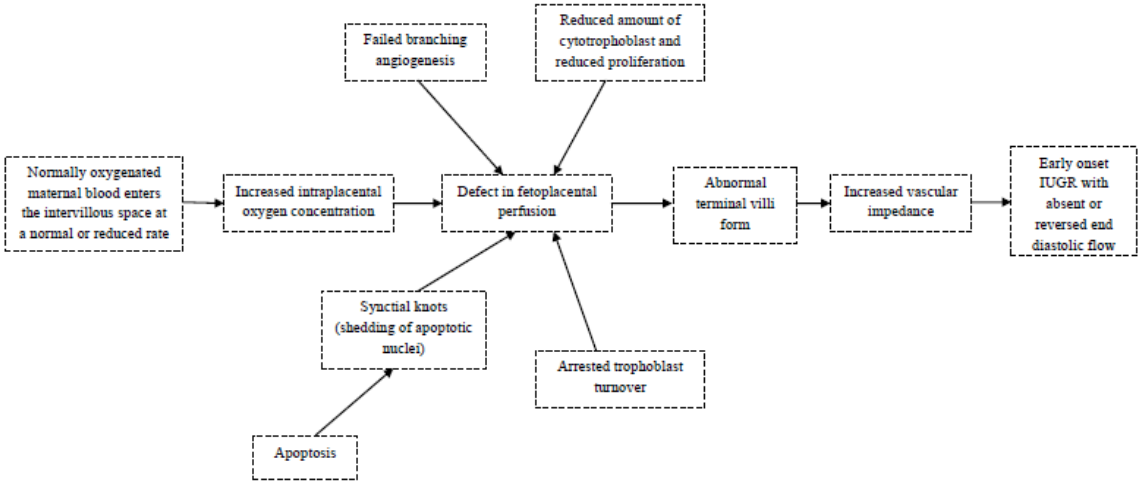
Appendix G: Preplacental Hypoxia Pathways



Appendix H: Uteroplacental Hypoxia Pathways



Appendix I: Postplacental Hypoxia Pathways



Appendix J: Calculations for the Removal of Birth Weights Three Standard Deviations from the Mean

J.1. Males Calculations

Gestational Week	Mean	Standard Deviation	3 SD's Below the Mean	3 SD's Above the Mean
22	507.07	48.56	361.40	652.74
23	622.72	82.59	374.96	870.49
24	651.85	81.45	407.50	896.19
25	747.82	143.02	318.75	1176.89
26	910.21	143.17	480.70	1339.72
27	1066.63	312.56	128.96	2004.31
28	1124.75	323.15	155.29	2094.21
29	1344.45	250.12	594.10	2094.80
30	1616.97	464.91	222.24	3011.71
31	1682.85	320.60	721.04	2644.66
32	1861.19	357.40	789.01	2933.38
33	2184.94	430.18	894.40	3475.48
34	2426.94	481.33	982.94	3870.93
35	2637.10	444.17	1304.60	3969.60
36	2903.94	461.97	1518.04	4289.84
37	3137.07	479.18	1699.52	4574.63
38	3376.84	461.46	1992.46	4761.23
39	3527.79	446.39	2188.63	4866.95
40	3686.96	442.43	2359.66	5014.26
41	3806.74	449.57	2458.02	5155.46
42	3948.84	532.46	2351.47	5546.20

J.2. Females Calculations

Gestational Week	Mean	Standard Deviation	3 SD's Below the Mean	3 SD's Above the Mean
22	432.89	68.95	226.04	639.74
23	542.62	81.20	299.01	786.22
24	594.46	77.89	360.79	828.12
25	795.53	205.16	180.05	1411.01
26	878.03	179.77	338.71	1417.34
27	958.51	218.68	302.49	1614.54
28	1118.46	198.04	524.35	1712.57
29	1220.42	265.88	422.78	2018.07
30	1388.42	320.18	427.88	2348.96
31	1626.87	270.82	814.42	2439.31
32	1777.17	335.55	770.52	2783.83
33	2069.75	383.85	918.19	3221.30
34	2278.60	455.73	911.41	3645.79
35	2581.60	458.61	1205.76	3957.44
36	2805.16	495.61	1318.34	4291.99
37	3044.04	474.75	1619.80	4468.28
38	3259.82	448.94	1912.99	4606.66
39	3404.52	426.01	2126.48	4682.57
40	3548.62	431.27	2254.80	4842.44
41	3643.93	437.09	2332.67	4955.20
42	3732.27	433.71	2431.14	5033.40

Appendix K: Macro for Quantile Regression

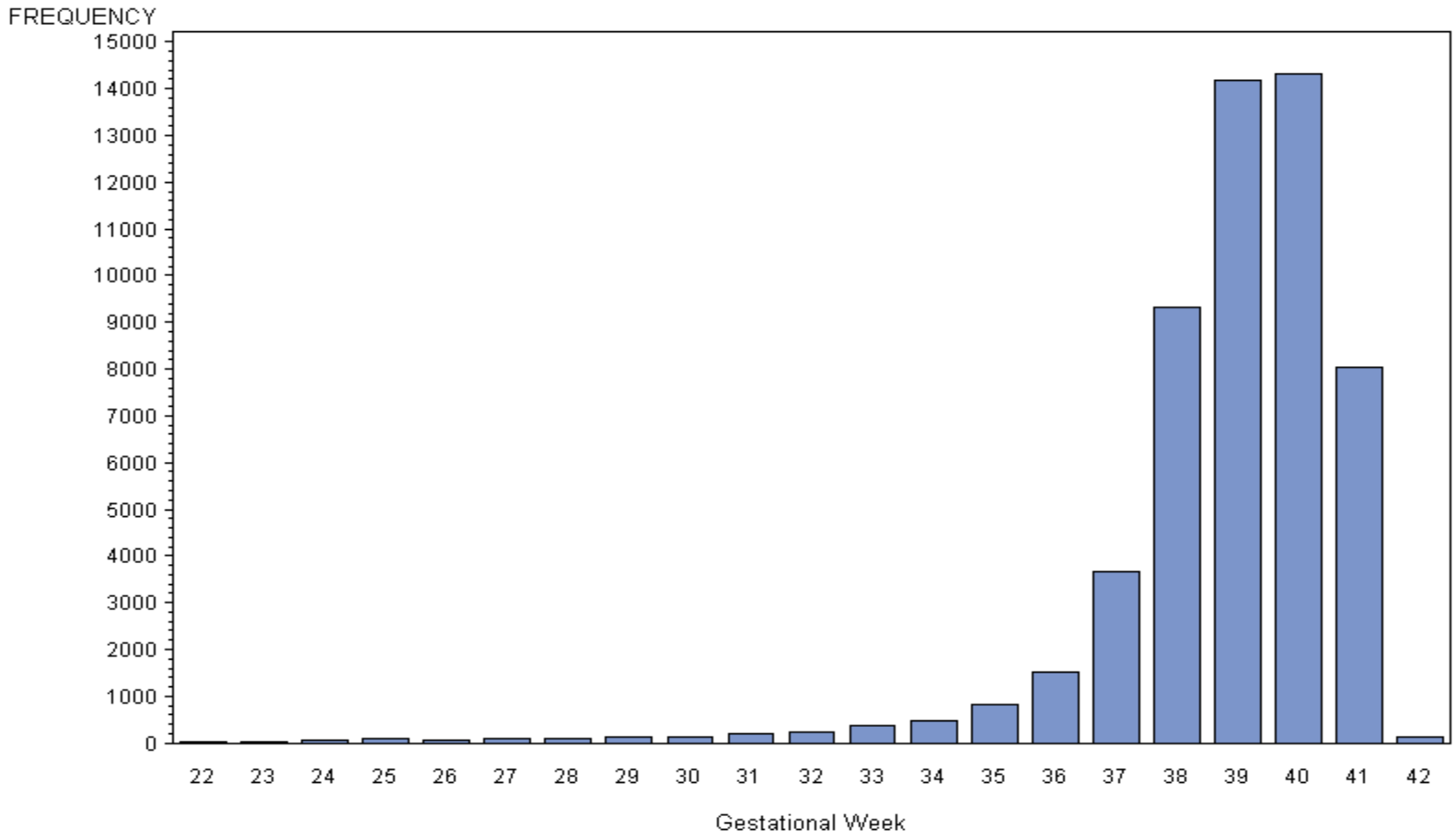
```
ods graphics on;
ods html;

%macro quantiles(NQuant, Quantiles);
%do i=1 %to &NQuant;
proc quantreg data=x4 algorithm=INTERIOR(TOLERANCE=1E-4
KAPPA=0.25)PLOT=FITPLOT(NODATA);
model fpratio = GESTWK GESTWK*GESTWK/ quantile=%scan(&quantiles,&i,",");
output out=outp&i pred=p&i;
run;
%end;
%mend;

%let quantiles = %str(.03,.05,.10,.25,.5,.75,.90,.95,.97);
%quantiles(10,&quantiles);

ods graphics off;
ods html close;
```

Appendix L: Descriptive Statistics for Sample: Binary, Categorical and Continuous Variables

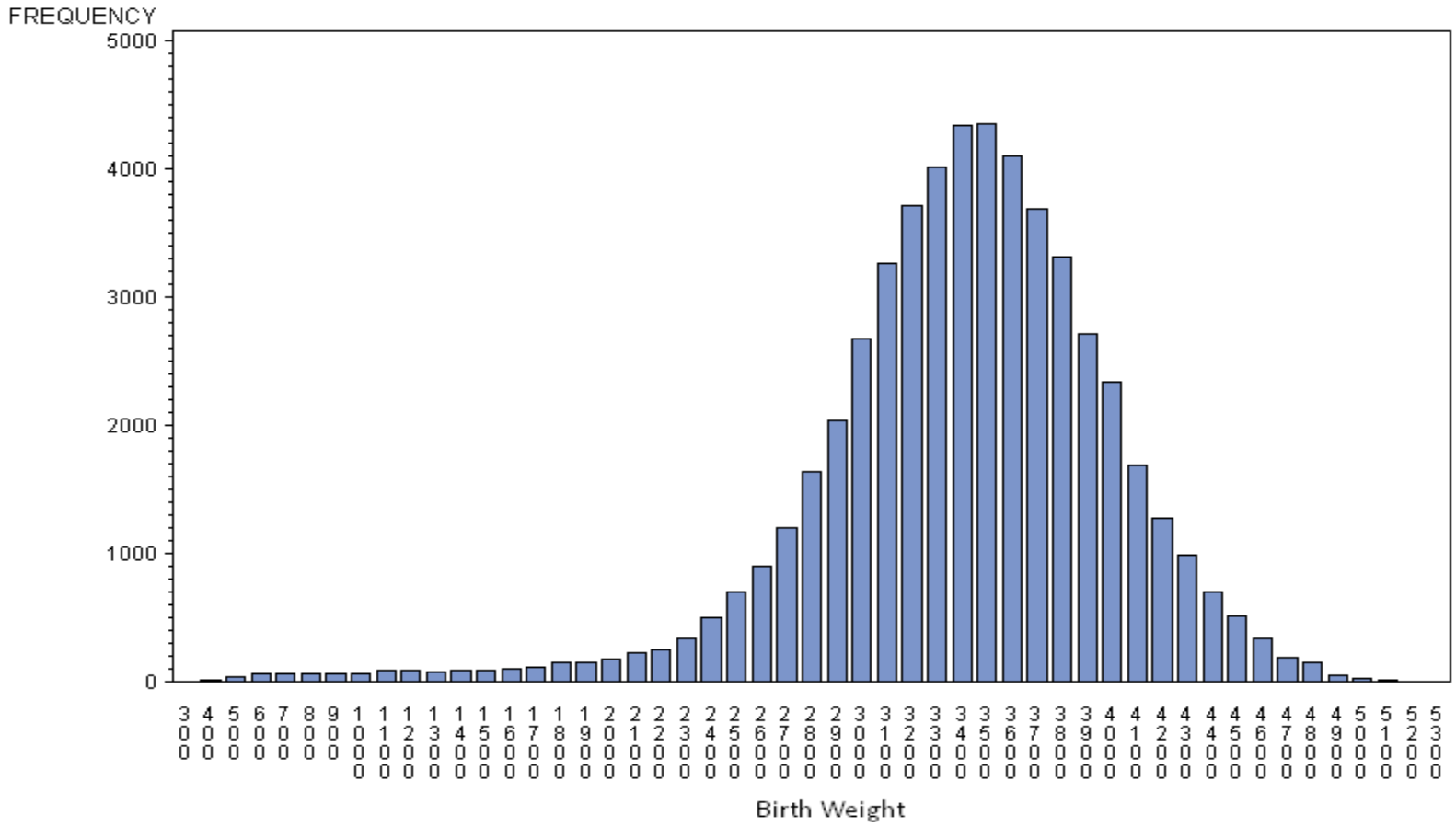
Predictor Variables (Binary/Categorical)		n	Frequency (%)	Missing
Parity	0	53954	23968(44.42)	3
	≥1		29985(55.58)	
Smoking during Pregnancy	No	53954	44986(83.38)	2
	Yes		8968(16.62)	
Gestational Hypertension/Preeclampsia	No	53943	49169(91.15)	13
	Preeclampsia		1827(3.39)	
	Gestational Hypertension		2947(5.46)	
Body Mass Index	≤18.5 kg/m^2	53956	19696 (36.50)	0
	18.5-24.9 kg/m^2		19856(36.80)	
	25.0-29.9 kg/m^2		8675(16.08)	
	>30.0 kg/m^2		5729(10.62)	
Anaemia	No	26674	25710(96.51)	27316
	Yes		930(3.49)	
Sex	Male	53956	27636(51.22)	0
	Female		26320 (48.78)	
Maternal Asthma	No	53956	52748(97.76)	0
	Yes		1208(2.24)	
Placenta Delivery	Spontaneous	53411	40246(75.34)	547
	Expressed or assisted		280(5.24)	
	Manual		10095(18.90)	
	Retained		270(0.52)	
Placenta Previa	No	53956	53579(99.30)	0
	Yes		377(0.70)	
Placental Abruption	No	53956	52776(97.80)	0
	Yes		1180(2.20)	
Gestational Diabetes	No	53952	50834(94.22)	4
	Yes		3118(5.78)	
Cord Complication	No	53956	37220(68.98)	0
	Cord around the neck or body, knot in the cord, prolapsed or lacerated cord		16259(30.13)	

	Short, 2-vessel or velamentous cord		477(0.88)	
Gestational Weight Gain	Normal <10lb at 30 weeks or <20 lbs at term >40 lbs at term	53956	46802(86.74) 1514(2.81) 5640(10.45)	
Birth Weight Category	SGA AGA LGA	53834	4259(7.91) 43697(81.17) 5878(10.92)	122
Predictor Variables (Continuous)		**n**	**Mean (±S.D.)**	**Missing**
Maternal Age *(years)*		52227	29.14(±5.11)	1729
Maternal Height *(inches)*		50534	64.80(±2.47)	3422

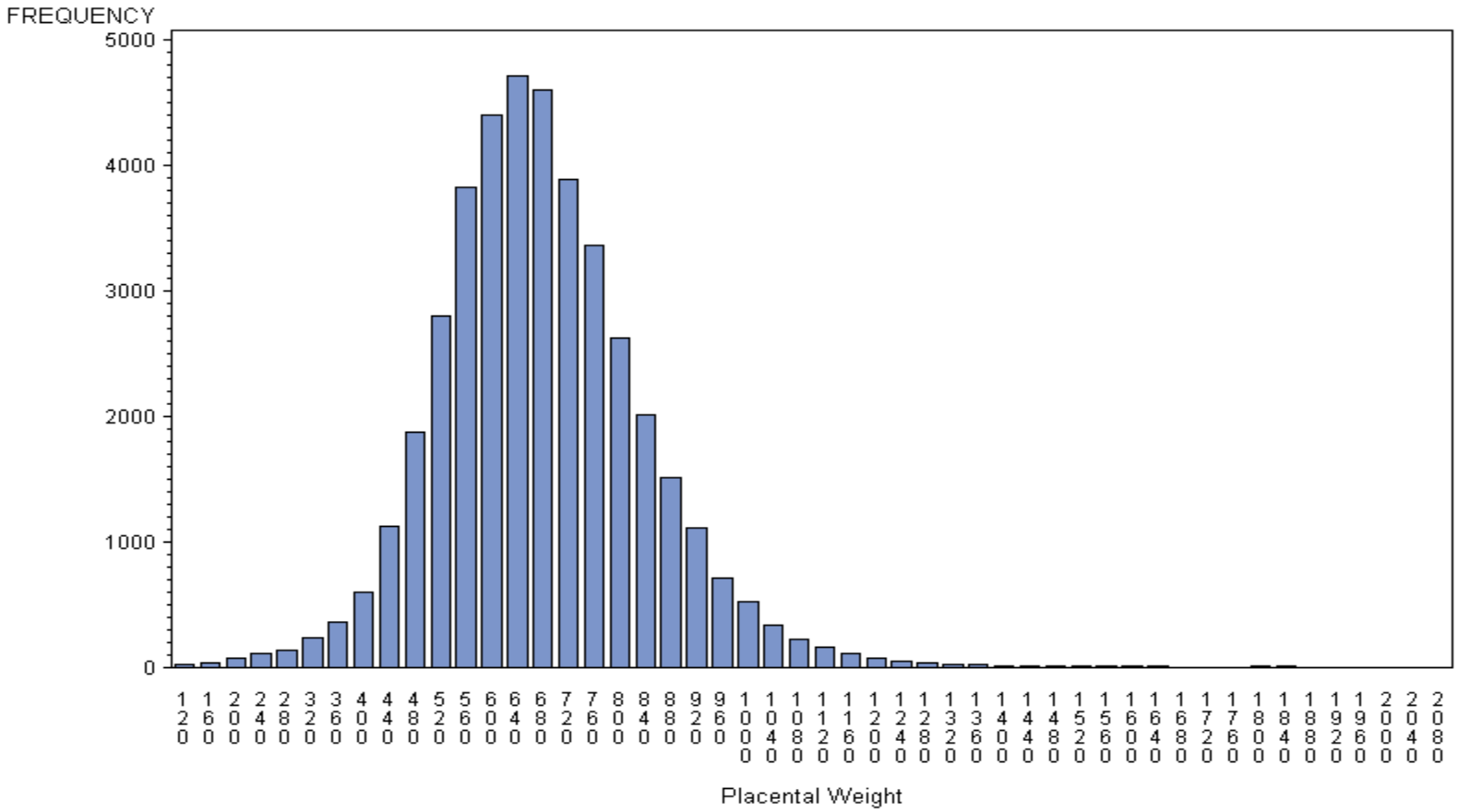
Appendix M: Distributions of Key Variables
M.1. Gestational Age Distribution



M.2. Birth Weight Distribution



M.3. Placenta Weight Distribution



Appendix N: Detailed Description of SGA and LGA Placental Weight Ratios

N.1. Description of SGA PWR Curves

Infants were defined as SGA based on Kramer's gestational age and sex specific standards. There are 1677 males and 1533 females who are included in the analysis after the exclusion criteria were applied and missing data were removed. The 3rd percentile reached statistical significance at $p<0.05$, the 5th at $p<0.01$ and the remaining percentiles at $p<0.001$. The median gestational age was 39 weeks for both males and females which was the same as for the overall population. The mean gestational ages for males and females are 38.5 (SD=2.49) and 37.5(2.34) respectively. While the mean gestational ages are similar to that of the overall population, the standard deviations were larger for the SGA group.

Males have a mean PWR of 0.2036 (SD=0.0537) and a median PWR of 0.1955. The means at the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th are 0.1391, 0.14500.1562, 0.1756, 0.1986. 0.2242, 0.2559, 0.2794 and 0.2950. Females have a mean PWR of 0.2059 (SD=0.0516) and a median PWR of 0.1990. The means at the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th are 0.1434, 0.1503, 0.1623, 0.1792, 0.2011, 0.2260, 0.2575, 0.2803 and 0.2979. Again the PWR decreases as gestational age increases and there was more dispersion in the lower gestational ages than at the higher gestational ages for both males and females.

Through examination of Table 4.5 and 4.6, which show the exact PWR at each gestational age by percentile, it was evident that the SGA infants have higher PWR's than the overall population. Similar to the overall population, the females have higher PWR's than males, yet not significantly different from each other. Again, there was more dwaspersion at the lower gestational ages for both males and females. There was a greater range of PWR values at the 50th percentile for males than females. The range for the PWR between 22 and 42 weeks at the 50th percentile was 0.3171 and 0.3021 for males and females respectively. The same pattern of a higher range of PWR's at particular percentile for males than females also holds true for extremes, as shown in the 10th and 90th percentile.

N.2. Description of LGA PWR Curves

Infants were defined as LGA based on Kramer's gestational age and sex specific standards. There are 2566 males and 1813 females who are included in the analysis after the exclusion criteria were applied and the missing data were removed. The median gestational age for males was 39 weeks and for females it was 40 weeks. The mean gestational age for males was 38.8 weeks (SD=2.06) and 38.9 weeks (SD=2.05) for females. The range of gestational ages for females was between 25 and 42 weeks, and for males it was between 23 and 42 weeks. Statistically significance was not achieved at a level of $p<0.05$ for the 3^{rd} and 5^{th} percentiles for both males and females, therefore, they were not included.

Males have a median PWR of 0.1956 and a mean PWR of 0.1998 (SD=0.0374). The means at the 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, 97^{th} are 0.1602, 0.1776, 0.1947, 0.2188, 0.2403, 0.2576 and 0.2685 respectively. Females have a median PWR of 0.2020 and a mean PWR of 0.2072 (SD=0.0422). The means at the 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, 97^{th} are 0.1649, 0.1816, 0.2043, 0.2293, 0.2523, 0.2700 and 0.2868 respectively.

Again, females had higher PWR's than males across percentiles, but the difference was not significant. There was a greater range in PWR's at the 50^{th} percentile across gestations for females than for males. Furthermore, this pattern holds true at the extreme percentiles. There was a greater range in PWR's between the 25^{th} and 42^{nd} week of gestation at the 10^{th} and 90^{th} percentile in females than in males. The graphical representation for these distributions can be found in Figure 4.10 and 4.11, and the exact values for each percentile by gestational age can be found in Table 4.9 and 4.10.

N.3. Differences between SGA, AGA and LGA Curves

The figures below show graphically how the PWR changes across gestation between SGA, AGA and LGA infants at the median. Specifically, they show that there was a greater dispersion in the PWR in SGA infants than in AGA and LGA infants, especially in the lower gestational ages. The range of PWR's between the 3^{rd} and 97^{th} percentiles at 22 and 23 weeks for male SGA infants was 0.7295 and 0.6640 respectively. The range of PWR's between the 3^{rd} and 97^{th} percentiles at 22 and 23 weeks for female

SGA infants was 0.8513 and 0.7758 respectively. However, the range of PWR's between the 3rd and 97th percentiles at 22 and 23 weeks for male AGA infants was 0.4776 and 0.440 respectively. Also, the range of PWR's between the 3rd and 97th percentiles at 22 and 23 weeks for female AGA infants was 0.6073 and 0.5567 respectively. Therefore, it was evident that there was more dispersion in the PWR's at the earlier gestations in SGA infants than in AGA infants. To provide a similar comparison, the range of values between the 10th and 97th percentile for LGA male infants at 22 and 23 weeks gestation are 0.2196 and 0.1782. The ranges for female LGA infants between the 10th and 97th percentiles at 22 and 23 weeks are 0.4778 and 0.4315 respectively. Comparing these results to the male and female AGA ranges for between the 10th and 97th percentile, the dispersion in LGA infants was less than in AGA infants. It can then be concluded that the dispersion at the lower gestational ages was greatest in SGA infants than in both LGA and AGA infants. When comparison was made between LGA and AGA infants the AGA infants show more dispersion at the lower gestational ages than do the LGA infants.

Furthermore, at the earlier gestational ages both male and female SGA infants have higher PWR's than male and female AGA and LGA infants. The differences in PWR's were the most pronounced at the higher percentiles and at the earlier gestational ages. SGA infants had much higher PWR's in early gestation than both SGA and AGA infants at the early gestation. At the 90th, 95th and 97th percentile SGA infants have PWR's that were a lot higher than the AGA and LGA infants. On the other hand, LGA infants have lower PWR's at the lower gestational ages when compared to AGA infants.

N.4. SGA Male Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.2987	0.2954	0.3157	0.3971	0.5085	0.5673	0.7931	0.9229	1.0282
23	0.2827	0.2805	0.2995	0.3736	0.4749	0.5320	0.7346	0.8533	0.9467
24	0.2675	0.2664	0.2842	0.3515	0.4431	0.4986	0.6794	0.7877	0.8699
25	0.2531	0.2531	0.2696	0.3306	0.4132	0.4670	0.6275	0.7258	0.7978
26	0.2394	0.2404	0.2559	0.3109	0.3852	0.4372	0.5788	0.6679	0.7303
28	0.2146	0.2172	0.2310	0.2754	0.3348	0.3831	0.4912	0.5634	0.6093
29	0.2034	0.2067	0.2197	0.2596	0.3124	0.3588	0.4523	0.5170	0.5558
30	0.1930	0.1970	0.2093	0.2450	0.2919	0.3363	0.4167	0.4744	0.5070
31	0.1834	0.1879	0.1997	0.2316	0.2732	0.3156	0.3843	0.4357	0.4629
32	0.1745	0.1796	0.1909	0.2196	0.2564	0.2968	0.3552	0.4007	0.4234
32	0.1745	0.1796	0.1909	0.2196	0.2564	0.2968	0.3552	0.4007	0.4234
33	0.1665	0.1719	0.1829	0.2087	0.2415	0.2798	0.3294	0.3697	0.3886
34	0.1593	0.1650	0.1758	0.1992	0.2285	0.2646	0.3069	0.3425	0.3585
35	0.1529	0.1589	0.1694	0.1909	0.2173	0.2512	0.2876	0.3191	0.3330
36	0.1473	0.1534	0.1639	0.1838	0.2080	0.2396	0.2716	0.2996	0.3122
37	0.1425	0.1487	0.1592	0.1780	0.2005	0.2299	0.2588	0.2839	0.2961
38	0.1384	0.1446	0.1553	0.1735	0.1950	0.2220	0.2494	0.2721	0.2847
39	0.1352	0.1413	0.1522	0.1702	0.1913	0.2159	0.2432	0.2641	0.2779
40	0.1328	0.1387	0.1500	0.1682	0.1895	0.2116	0.2402	0.2600	0.2758
41	0.1312	0.1369	0.1486	0.1675	0.1895	0.2092	0.2405	0.2597	0.2783
42	0.1304	0.1357	0.1480	0.1680	0.1914	0.2085	0.2441	0.2633	0.2856

N.5. SGA Female Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	3rd Percentile	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
22	0.3107	0.3079	0.3692	0.4060	0.4924	0.5633	0.7303	1.1694	1.1620
23	0.2923	0.2909	0.3479	0.3825	0.4623	0.5280	0.6817	1.0716	1.0681
24	0.2749	0.2749	0.3278	0.3603	0.4338	0.4946	0.6355	0.9794	0.9794
25	0.2586	0.2598	0.3087	0.3393	0.4068	0.4631	0.5919	0.8927	0.8960
26	0.2433	0.2457	0.2908	0.3196	0.3814	0.4334	0.5509	0.8116	0.8178
27	0.2291	0.2324	0.2739	0.3011	0.3577	0.4057	0.5124	0.7360	0.7450
28	0.2159	0.2202	0.2582	0.2838	0.3354	0.3798	0.4764	0.6660	0.6773
29	0.2038	0.2088	0.2436	0.2677	0.3148	0.3558	0.4430	0.6016	0.6150
30	0.1927	0.1984	0.2301	0.2529	0.2958	0.3337	0.4121	0.5427	0.5579
31	0.1827	0.1890	0.2177	0.2393	0.2783	0.3134	0.3837	0.4894	0.5060
32	0.1737	0.1805	0.2064	0.2269	0.2624	0.2951	0.3579	0.4416	0.4595
33	0.1657	0.1729	0.1962	0.2158	0.2481	0.2786	0.3346	0.3994	0.4182
34	0.1588	0.1663	0.1871	0.2058	0.2353	0.2640	0.3138	0.3627	0.3821
35	0.1530	0.1606	0.1791	0.1971	0.2242	0.2513	0.2956	0.3316	0.3513
36	0.1482	0.1558	0.1722	0.1897	0.2146	0.2405	0.2799	0.3060	0.3258
37	0.1445	0.1520	0.1664	0.1834	0.2066	0.2316	0.2668	0.2860	0.3055
38	0.1418	0.1491	0.1618	0.1784	0.2002	0.2245	0.2562	0.2716	0.2905
39	0.1401	0.1472	0.1582	0.1747	0.1953	0.2193	0.2481	0.2627	0.2808
40	0.1395	0.1462	0.1557	0.1721	0.1921	0.2161	0.2426	0.2593	0.2763
41	0.1399	0.1461	0.1544	0.1708	0.1904	0.2146	0.2396	0.2616	0.2771
42	0.1414	0.1470	0.1542	0.1707	0.1903	0.2151	0.2392	0.2693	0.2832

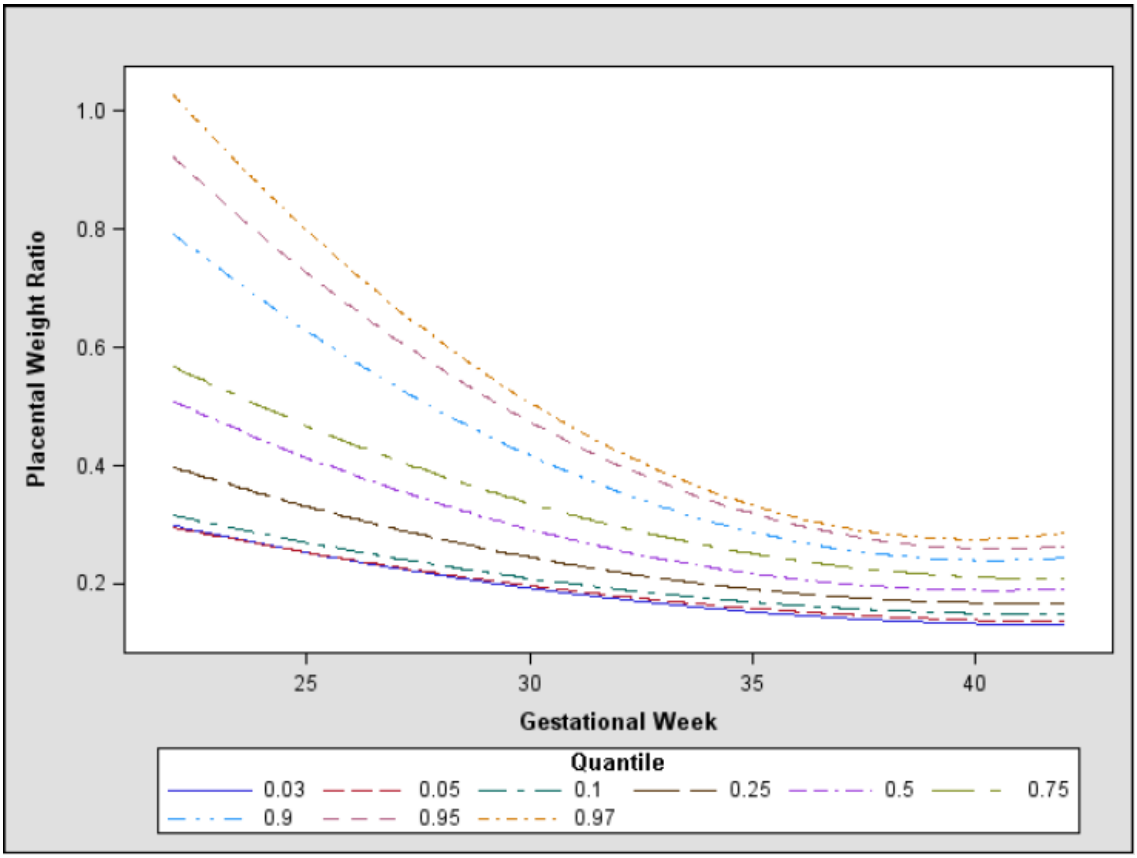
N.6. LGA Male Placental Weight Ratios Gestational Age for the 3rd through the 97th Percentile

Gestational Age	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
23	0.2513	0.3199	0.3673	0.4110	0.4568	0.4690	0.4710
25	0.2352	0.2928	0.3360	0.3745	0.4170	0.4295	0.4295
26	0.2276	0.2802	0.3214	0.3576	0.3984	0.4111	0.4104
27	0.2203	0.2682	0.3075	0.3415	0.3808	0.3936	0.3925
28	0.2134	0.2569	0.2942	0.3263	0.3639	0.3770	0.3757
29	0.2068	0.2463	0.2817	0.3119	0.3480	0.3614	0.3600
30	0.2005	0.2363	0.2699	0.2984	0.3330	0.3466	0.3455
31	0.1946	0.2269	0.2588	0.2858	0.3188	0.3327	0.3321
32	0.1890	0.2182	0.2483	0.2741	0.3055	0.3198	0.3198
33	0.1837	0.2101	0.2386	0.2632	0.2931	0.3077	0.3086
34	0.1787	0.2027	0.2296	0.2531	0.2816	0.2966	0.2986
35	0.1741	0.1960	0.2212	0.2440	0.2709	0.2863	0.2897
36	0.1698	0.1899	0.2136	0.2356	0.2611	0.2770	0.2819
37	0.1658	0.1844	0.2067	0.2282	0.2523	0.2686	0.2752
38	0.1622	0.1796	0.2004	0.2216	0.2442	0.2610	0.2697
39	0.1588	0.1755	0.1949	0.2159	0.2371	0.2544	0.2653
40	0.1559	0.1720	0.1900	0.2110	0.2309	0.2487	0.2620
41	0.1532	0.1691	0.1859	0.2070	0.2255	0.2439	0.2599
42	0.1509	0.1669	0.1824	0.2039	0.2210	0.2400	0.2589

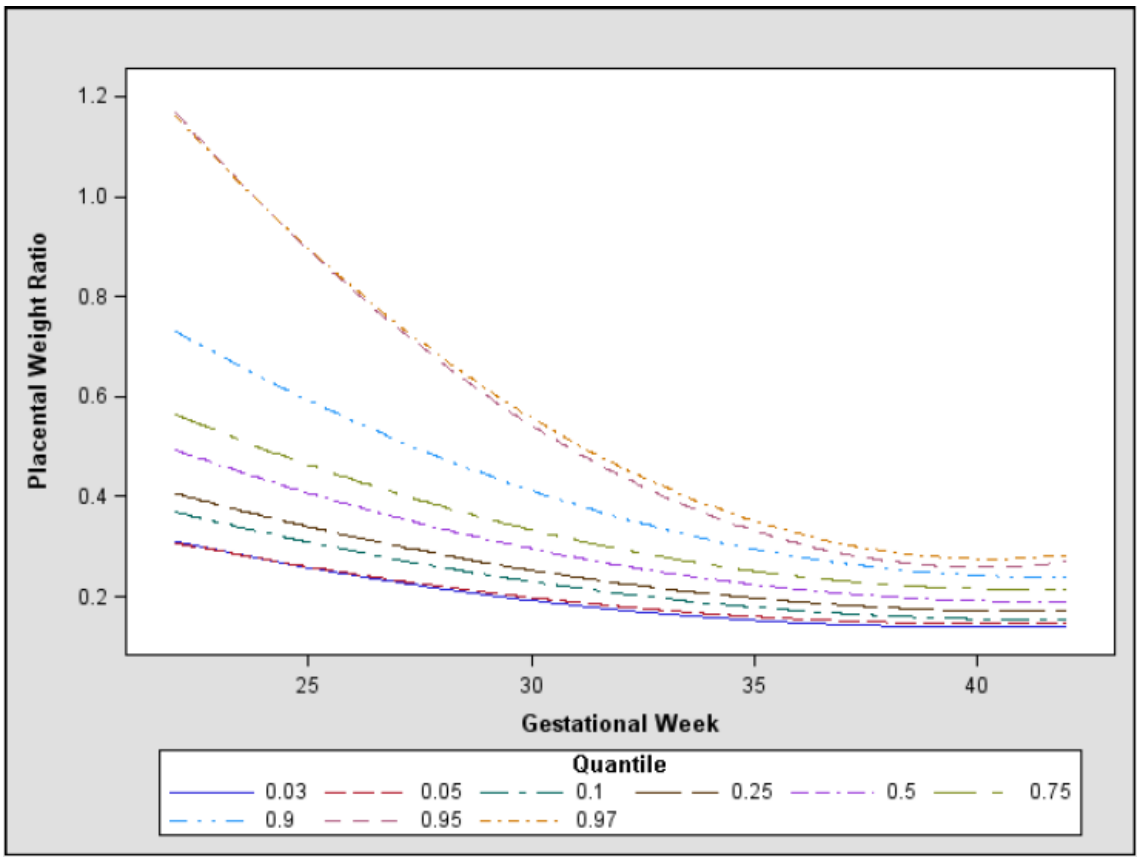
N.7. LGA Female Placental Weight Ratios by Gestational Age for the 3rd through the 97th Percentile

Gestational Age	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile	97th Percentile
25	0.2835	0.3131	0.3782	0.4769	0.5365	0.6261	0.7623
26	0.2711	0.2988	0.3581	0.4475	0.5020	0.5836	0.7026
27	0.2593	0.2853	0.3391	0.4199	0.4697	0.5435	0.6467
28	0.2480	0.2725	0.3212	0.3940	0.4395	0.5061	0.5947
29	0.2374	0.2604	0.3045	0.3699	0.4114	0.4712	0.5465
30	0.2273	0.2490	0.2890	0.3476	0.3854	0.4389	0.5022
31	0.2178	0.2384	0.2746	0.3270	0.3616	0.4091	0.4618
32	0.2089	0.2285	0.2614	0.3081	0.3398	0.3819	0.4253
33	0.2006	0.2193	0.2494	0.2910	0.3202	0.3573	0.3926
34	0.1929	0.2109	0.2385	0.2756	0.3027	0.3353	0.3638
35	0.1857	0.2031	0.2287	0.2620	0.2874	0.3158	0.3388
36	0.1792	0.1961	0.2201	0.2501	0.2741	0.2989	0.3177
37	0.1732	0.1899	0.2127	0.2399	0.2630	0.2846	0.3005
38	0.1679	0.1844	0.2064	0.2316	0.2540	0.2728	0.2872
39	0.1631	0.1796	0.2013	0.2249	0.2471	0.2636	0.2777
40	0.1589	0.1755	0.1973	0.2200	0.2423	0.2570	0.2721
41	0.1553	0.1721	0.1945	0.2169	0.2396	0.2529	0.2703
42	0.1523	0.1695	0.1929	0.2155	0.2391	0.2514	0.2724

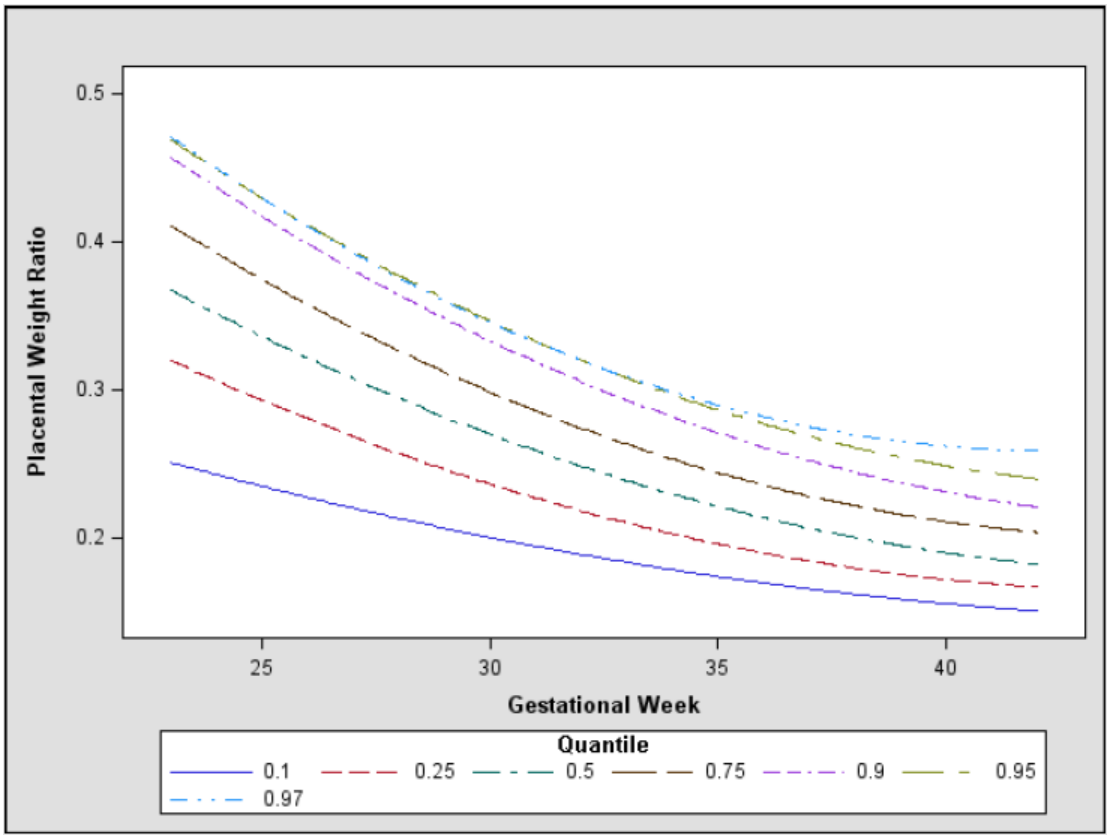
N.8. SGA Male Placental Weight Ratio Distributions by Gestational Age



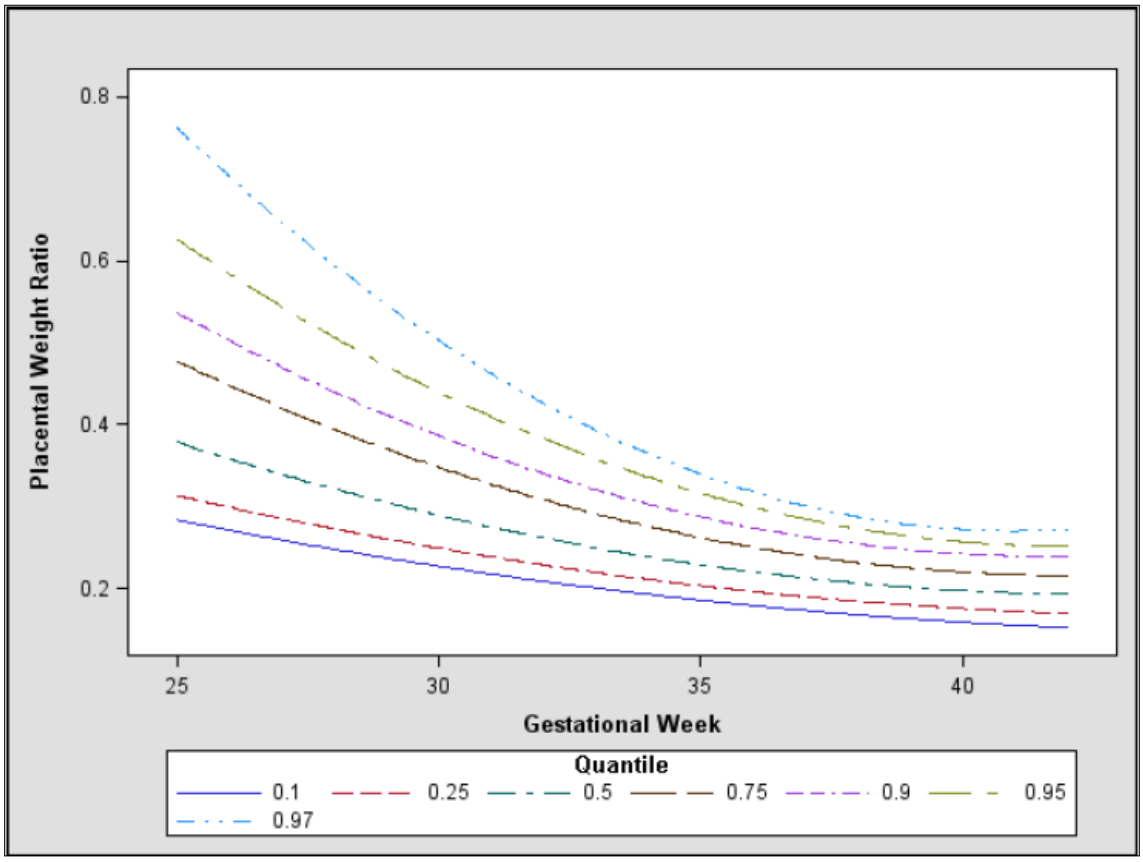
N.9. SGA Female Placental Weight Ratio Distributions by Gestational Age



N.10. LGA Male Placental Weight Ratio Distributions by Gestational Age



N.11. LGA Female Placental Weight Ratio Distributions by Gestational Age



Appendix O: Results of Interaction Terms between Smoking and Preeclampsia with Gestational Age Category

O.1. Interaction Terms and Significance Levels

Effect	Degrees of Freedom	Wald Chi-Square	P-value
Gestational Age Category	4	1.95	0.7446
Preeclampsia	2	38.51	0.0001
Smoking	2	250.98	0.0001
Gestational Age Category x Preeclampsia	4	9.90	0.0420
Gestational Age Category x Smoking	4	9.52	0.0494

Appendix P: Full Blocked Logistic Regression Models of Baseline and Pregnancy Factors Hypothesized to Influence a PWR
P.1. Blocked Logistic Regression Model of Baseline and Pregnancy Factors Hypothesized to Influence a Placental Weight Ratio ≤10th Percentile for Infants Born at ≥37 Weeks

	Odds Ratio (95% Confidence Interval)					
			Blockwise Model Building at p<.20		***Restricted to p<.05***	
Predictors	**Univariable**	**Model 1[1]**	**Model 2[2]**	**Model 3[3]**	**Model 4[4]**	**Final Model[5]**
Parity						
0	-	-	-	-	-	X
≥1	0.915 (0.832, 1.006)*	0.886 (0.800, 0.980)**	0.909 (0.826, 1.001)*	0.913 (0.829, 1.005)*	0.928 (0.841, 1.024)*	
Smoking During Pregnancy						
No *(ref)*	-	-	-	-	-	-
Yes	0.647 (0.559, 0.749)*	0.664 (0.568, 0.776)**	0.631 (0.543, 0.733)**	0.630 (0.542, 0.732)**	0.609 (0.522, 0.711)**	0.612 (0.527, 0.711)**
Maternal Asthma						
No *(ref)*	-	X	X	X	X	X
Yes	0.809 (0.642, 1.020)					
Maternal Age						
<21 years	0.881 (0.736, 1.055)					
21-34 years*(ref)*	-	X	X	X	X	X
>34 years	1.079 (0.949, 1.226)					
Maternal Height *For every 10cm increase*	1.013 (0.993, 1.033)	X	X	X	X	X
Pre-pregnancy BMI						
≤18.5 kg/m^2	0.923 (0.829, 1.027)	0.901 (0.806, 1.008)*	0.934 (0.838, 1.041)*	0.933 (0.837, 1.039)*	0.907 (0.811, 1.014)*	0.925 (0.829, 1.032)*
18.5-24.9 kg/m^2 *(ref)*	-	-	-	-	-	-
25.0-29.9 kg/m^2	0.827 (0.709, 0.965)*	0.820 (0.702, 0.957)**	0.826 (0.707, 0.966)**	0.826 (0.707, 0.965)**	0.813 (0.694, 0.953)**	0.817 (0.698, 0.956)**
>30.0 kg/m^2	0.805 (0.670, 0.967)*	0.798 (0.662, 0.961)**	0.811 (0.673, 0.978)**	0.813 (0.674, 0.980)**	0.806 (0.666, 0.975)**	0.826 (0.685, 0.996)**

Preeclampsia No *(ref)* Preeclampsia	- 0.707 (0.533, 0.937)*		- 0.985 (0.695, 1.398)[6]	- 0.990 (0.697, 1.405)[6]	- 0.999 (0.703, 1.420)[6]	- 0.998 (0.703, 1.417)[6]
Gestational Diabetes No *(ref)* Yes	- 0.979 (0.691, 1.387)		- 0.737 (0.555, 0.979)**	- 0.735 (0.553, 0.976)**	- 0.734 (0.551, 0.979)**	- 0.729 (0.547, 0.971)**
Placental Previa No *(ref)* Yes	- 0.747 (0.344, 1.619)			X	X	X
Placental Abruption No *(ref)* Yes	- 1.223 (0.795, 1.881)			- 1.229 (0.791, 1.909)[6]	- 1.231 (0.792, 1.914)[6]	- 1.273 (0.826, 1.963)[6]
Cord Complications None *(ref)* Cord around the neck or body, knot in the cord, prolapsed or lacerated cord Short, 2-vessel or velamentous cord	- 0.810 (0.728, 0.901)* 1.990 (1.390, 2.850)*			- 0.815 (0.731, 0.908)** 1.989 (1.381, 2.864)*	- 0.821 (0.735, 0.916)** 1.932 (1.338, 2.790)**	- 0.816 (0.730, 0.912)** 1.969 (1.369, 2.831)**
Gestational Weight Gain <10lb at 30 weeks or <20 lbs at term Normal *(ref)* >40 lbs at term	0.713 (0.427, 1.190) - 0.821 (0.690, 0.977)				X	X
Birth Weight Category SGA	1.130				1.153	1.180

	(0.952, 1.342)				(0.963, 1.381)*	(0.990, 1.408)*
AGA *(ref)*	-				-	-
LGA	0.829 (0.701, 0.981)*				0.824 (0.693, 0.980)**	0.811 (0.683, 0.962)**
Anaemia						
No *(ref)*	-				-	-
Yes	0.767 (0.560, 1.052)				0.787 (0.569, 1.089)[6]	0.768 (0.557, 1.057)*
Placental Delivery						
Spontaneous *(ref)*	-				-	-
Expressed or assisted	1.186 (1.006, 1.397)*				1.163 (0.982, 1.376)*	1.183 (1.001, 1.398)**
Manual	1.108 (0.987, 1.244)*				1.104 (0.981, 1.243)*	1.119 (0.995, 1.258)
Retained	3.832 (2.344, 6.264)*				4.053 (2.461, 6.675)**	4.022 (2.446, 6.612)**

[1]-Baseline Factors; [2]-Baseline +Mid-Pregnancy Factors; [3]-Cord and Placental Complications; [4]-Late and Post-Pregnancy Factors; [5]-Only Factors with a significance level of $p<0.05$;[6]-Variable remains in model despite not reaching statistical significance for the specified level of the outcome because for the other level of the outcome it reaches statistical significance; *-Covariates with a significance level of $p<0.20$; **-Covariates with a significance level of $p<0.05$

P.2. Blocked Logistic Regression Model of Baseline and Pregnancy Factors Hypothesized to Influence a Placental Weight Ratio ≥90th Percentile for Infants Born at ≥37 Weeks

	Odds Ratio (95% Confidence Interval)					
		Blockwise Model Building at p<.20				***Restricted to p<.05***
Predictors	**Univariable**	**Model 1[1]**	**Model 2[2]**	**Model 3[3]**	**Model 4[4]**	**Final Model[5]**
Parity						
0	-	-	-	-	-	X
≥1	1.073 (0.979, 1.176)	1.074 (0.972, 1.187)*	1.087 (0.989, 1.195)*	1.087 (0.989, 1.195)*	1.067 (0.969, 1.176)*	
Smoking During Pregnancy						
No *(ref)*	-	-	-	-	-	-
Yes	1.795 (1.616, 1.994)*	1.767 (1.576, 1.981)**	1.805 (1.619, 2.011)**	1.794 (1.609, 1.999)**	1.808 (1.618, 2.019)**	1.798 (1.615, 2.001)**
Maternal Asthma						
No *(ref)*	-	X	X	X	X	X
Yes	1.085 (0.890, 1.322)					
Maternal Age						
<21 years	1.217 (1.042, 1.421)*	X	X	X	X	X
21-34 years*(ref)*	-					
>34 years	0.998 (0.877, 1.136)					
Maternal Height *For every 10cm increase*	1.001 (0.982, 1.020)	X	X	X	X	X
Pre-pregnancy BMI						
≤18.5 kg/m^2	1.296 (1.161, 1.446)**	1.272 (1.134, 1.426)**	1.260 (1.127, 1.410)**	1.268 (1.133, 1.418)**	1.263 (1.126, 1.417)**	1.265 (1.132, 1.414)**
18.5-24.9 kg/m^2 *(ref)*	-	-	-	-	-	-
25.0-29.9 kg/m^2	1.218 (1.050, 1.413)**	1.250 (1.075, 1.453)**	1.221 (1.050, 1.421)**	1.219 (1.047, 1.418)**	1.223 (1.050, 1.426)**	1.217 (1.046, 1.414)**
>30.0 kg/m^2	1.522 (1.296, 1.787)**	1.477 (1.252, 1.742)**	1.409 (1.193, 1.664)**	1.409 (1.193, 1.664)**	1.402 (1.184, 1.661)**	1.448 (1.229, 1.708)**

Preeclampsia No *(ref)* Preeclampsia	- 1.513 (1.240, 1.846)*		- 1.757 (1.342, 2.301)**	- 1.743 (1.330, 2.283)**	- 1.684 (1.281, 2.213)**	- 1.661 (1.269, 2.174)**
Gestational Diabetes No *(ref)* Yes	- 1.775 (1.364, 2.309)*		- 1.441 (1.176, 1.765)**	- 1.434 (1.170, 1.757)**	- 1.442 (1.176, 1.770)**	- 1.433 (1.169, 1.756)**
Placental Previa No *(ref)* Yes	- 0.980 (0.507, 1.895)			X	X	X
Placental Abruption No *(ref)* Yes	- 2.077 (1.485, 2.903)*			- 2.062 (1.468, 2.896)**	- 2.084 (1.481, 2.931)**	- 2.034 (1.446, 2.858)**
Cord Complications None *(ref)* Cord around the neck or body, knot in the cord, prolapsed or lacerated cord Short, 2-vessel or velamentous cord	- 1.189 (1.080, 1.309)* 1.180 (0.753, 1.851)			- 1.182 (1.071, 1.304)** 1.106 (0.697, 1.757)	- 1.183 (1.071, 1.308)** 1.137 (0.715, 1.807)	- 1.180 (1.070, 1.301)** 1.172 (0.744, 1.845)
Gestational Weight Gain <10lb at 30 weeks or <20 lbs at term Normal *(ref)* >40 lbs at term	1.002 (0.654, 1.537) - 1.014 (0.868, 1.184)				X	X
Birth Weight Category						

SGA	1.242 (1.057, 1.461)*				1.109 (0.934, 1.317)*	1.126 (0.954, 1.328)*
AGA *(ref)*	-				-	-
LGA	1.096 (0.946, 1.270)				1.114 (0.955, 1.298)*	1.111 (0.955, 1.291)
Anaemia						
No *(ref)*	-				-	-
Yes	1.898 (1.538, 2.342)*				1.876 (1.507, 2.336)**	1.862 (1.503, 2.305)**
Placental Delivery						
Spontaneous *(ref)*	-				-	-
Expressed or assisted	0.915 (0.771, 1.086)				0.903 (0.755, 1.080)[6]	0.907 (0.761, 1.081)[6]
Manual	1.010 (0.903, 1.130)				0.979 (0.872, 1.100)[6]	0.972 (0.867, 1.090)[6]
Retained	1.450 (0.737, 2.854)*				1.400 (0.706, 2.776)[6]	1.337 (0.675, 2.649)[6]

[1]-Baseline Factors; [2]-Baseline +Mid-Pregnancy Factors; [3]-Cord and Placental Complications; [4]-Late and Post-Pregnancy Factors; [5]-Only Factors with a significance level of $p<0.05$;[6]-Variable remains in model despite not reaching statistical significance for the specified level of the outcome because for the other level of the outcome it reaches statistical significance; *-Covariates with a significance level of $p<0.20$; **-Covariates with a significance level of $p<0.05$

P.3. Blocked Logistic Regression Model of Baseline and Pregnancy Factors Hypothesized to Influence a Placental Weight Ratio ≤10th Percentile in Infants born between 32 and 37 Weeks

	Odds Ratio (95% Confidence Interval)					
		Blockwise Model Building at p<.20				***Restricted to p<.05***
Predictors	**Univariable**	**Model 1[1]**	**Model 2[2]**	**Model 3[3]**	**Model 4[4]**	**Final Model[5]**
Parity 0 ≥1	- 0.687 (0.435, 1.084)*	- 0.631 (0.388, 1.025)*	- 0.686 (0.432, 1.089)*	- 0.710 (0.446, 1.130)*	- 0.661 (0.412, 1.059)*	- 0.695 (0.440, 1.099)*
Smoking During Pregnancy No *(ref)* Yes	- 0.493 (0.256, 0.947)*	- 0.629 (0.322, 1.232)[6]	- 0.513 (0.266, 0.989)**	- 0.525 (0.272, 1.013)*	- 0.542 (0.278, 1.055)*	- 0.494 (0.257, 0.950)*
Maternal Asthma No *(ref)* Yes	- 0.965 (0.405, 2.298)	X	X	X	X	X
Maternal Age <21 years 21-34 years*(ref)* >34 years	0.265 (0.064, 1.104) - 1.283 (0.744, 2.211)	X	X	X	X	X
Maternal Height *For every 10cm increase*	1.027 (0.933, 1.130)	X	X	X	X	X
Pre-pregnancy BMI ≤18.5 kg/m^2 18.5-24.9 kg/m^2 *(ref)* 25.0-29.9 kg/m^2 >30.0 kg/m^2	1.018 (0.610, 1.698) - 0.807 (0.379, 1.718) 0.708 (0.263, 1.902)	X	X	X	X	X

Preeclampsia No *(ref)* Preeclampsia	- 0.194 (0.026, 1.422)		- 1.028 (0.473, 2.235)	- 0.927 (0.429, 2.006)*	- 0.835 (0.372, 1.878)[6]	X
Gestational Diabetes No *(ref)* Yes	- 1.028 (0.479, 2.206		X	X	X	X
Placental Previa No *(ref)* Yes	- 0.341 (0.046, 2.527)			X	X	X
Placental Abruption No *(ref)* Yes	- 0.523 (0.160, 1.705)			- 0.575 (0.175, 1.893)[6]	- 0.593 (0.179, 1.965)[6]	- 0.615 (0.295, 1.282)*
Cord Complications None *(ref)* Cord around the neck or body, knot in the cord, prolapsed or lacerated cord Short, 2-vessel or velamentous cord	- 0.973 (0.594, 1.592) 0.771 (0.092, 5.482)			- 0.966 (0.588, 1.587)[6] 0.716 (0.092, 5.564)[6]	- 0.919 (0.554, 1.525)[6] 0.637 (0.080, 5.078)[6]	X
Gestational Weight Gain <10lb at 30 weeks or <20 lbs at term Normal *(ref)* >40 lbs at term	0.579 (0.076, 4.398) - 0.474 (0.113, 1.993)				X	X
Birth Weight Category						X

SGA	1.444 (0.689, 3.026)				X	
AGA *(ref)*	-					
LGA	1.419 (0.738, 2.728)					
Anaemia						
No *(ref)*	-				-	X
Yes	0.799 (0.242, 2.643)				0.884 (0.263, 2.967)[6]	
Placental Delivery						
Spontaneous *(ref)*	-					
Expressed or assisted	1.131 (0.432, 2.963)				X	X
Manual	1.054 (0.630, 1.762)					
Retained	5.657 (1.374, 23.290)*					

[1]-Baseline Factors; [2]-Baseline +Mid-Pregnancy Factors; [3]-Cord and Placental Complications; [4]-Late and Post-Pregnancy Factors; [5]-Only Factors with a significance level of $p<0.05$;[6]-Variable remains in model despite not reaching statistical significance for the specified level of the outcome because for the other level of the outcome it reaches statistical significance; *-Covariates with a significance level of $p<0.20$; **-Covariates with a significance level of $p<0.05$

P.4. Blocked Logistic Regression Model of Baseline and Pregnancy Factors Hypothesized to Influence a Placental Weight Ratio ≥90th Percentile for Infants Born between 32 and 37 Weeks

	Odds Ratio (95% Confidence Interval)					
		Blockwise Model Building at p<.20				***Restricted to p<.05***
Predictors	**Univariable**	**Model 1[1]**	**Model 2[2]**	**Model 3[3]**	**Model 4[4]**	**Final Model[5]**
Parity						
0	-	-	-	-	-	-
≥1	1.686 (1.094, 2.598)*	1.571 (0.980, 2.517)*	1.774 (1.138, 2.764)**	1.644 (1.049, 2.575)**	1.612 (1.011, 2.570)**	1.674 (1.085, 2.583)**
Smoking During Pregnancy						
No *(ref)*	-	-	-	-	-	-
Yes	1.518 (0.970, 2.378)	1.388 (0.852, 2.261)	1.586 (1.007, 2.498)	1.509 (0.952, 2.393)*	1.583 (0.987, 2.540)*	1.488 (0.949, 2.334)*
Maternal Asthma						
No *(ref)*	-	X	X	X	X	X
Yes	1.075 (0.500, 2.308)					
Maternal Age						
<21 years	1.206 (0.596, 2.439)	X	X	X	X	X
21-34 years*(ref)*	-					
>34 years	1.291 (0.767, 2.173)*					
Maternal Height *For every 10cm increase*	1.034 (0.946, 1.131)	X	X	X	X	X
Pre-pregnancy BMI						
≤18.5 kg/m^2	1.494 (0.891, 2.505)	X	X	X	X	X
18.5-24.9 kg/m^2 *(ref)*	-					
25.0-29.9 kg/m^2	1.137 (0.549, 2.357)					
>30.0 kg/m^2	2.326 (1.141, 4.744)					

Preeclampsia No *(ref)* Preeclampsia	- 1.014 (0.424, 2.423)		- 2.103 (1.153, 3.837)*	- 1.969 (1.082, 3.582)*	- 1.938 (1.040, 3.610)**	X
Gestational Diabetes No *(ref)* Yes	- 1.834 (1.026, 3.276)*		X	X	X	X
Placental Previa No *(ref)* Yes	- 0.282 (0.038, 2.085)			X	X	X
Placental Abruption No *(ref)* Yes	- 2.268 (1.216, 4.229)*			- 1.965 (1.033, 3.740)**	- 1.991 (1.027, 3.861)**	- 2.038 (1.323, 3.138)**
Cord Complications None *(ref)* Cord around the neck or body, knot in the cord, prolapsed or lacerated cord Short, 2-vessel or velamentous cord	- 1.545 (1.001, 2.386) 3.622 (1.269, 10.338)*			- 1.511 (0.969, 2.357) 3.214 (1.096, 9.421)**	- 1.453 (0.918, 2.298)* 3.745 (1.240, 11.307)**	X
Gestational Weight Gain <10lb at 30 weeks or <20 lbs at term Normal *(ref)* >40 lbs at term	∞ (0, ∞) - 1.646 (0.752, 3.605)				X	X
Birth Weight Category					X	X

SGA	1.322 (0.654, 2.669)					
AGA *(ref)*	-					
LGA	1.462 (0.808, 2.647)					
Anaemia						
No *(ref)*	-				-	
Yes	2.420 (1.170, 5.008)*				2.068 (0.961, 4.448)*	X
Placental Delivery						
Spontaneous *(ref)*	-					
Expressed or assisted	1.393 (0.604, 3.212)				X	
Manual	1.329 (0.845, 2.090)					X
Retained	1.658 (0.196, 14.010)					

[1]-Baseline Factors; [2]-Baseline +Mid-Pregnancy Factors; [3]-Cord and Placental Complications; [4]-Late and Post-Pregnancy Factors; [5]-Only Factors with a significance level of $p<0.05$;[6]-Variable remains in model despite not reaching statistical significance for the specified level of the outcome because for the other level of the outcome it reaches statistical significance; *-Covariates with a significance level of $p<0.20$; **-Covariates with a significance level of $p<0.05$

P.5. Blocked Logistic Regression Model of Baseline and Pregnancy Factors Hypothesized to Influence a Placental Weight Ratio ≤10th Percentile in Infants born at ≤32 Weeks

	Odds Ratio (95% Confidence Interval)					
		Blockwise Model Building at p<.20				***Restricted to p<.05***
Predictors	**Univariable**	**Model 1[1]**	**Model 2[2]**	**Model 3[3]**	**Model 4[4]**	**Final Model[5]**
Parity 0 ≥1	- 0.604 (0.339, 1.077)*	- 0.544 (0.290, 1.020)*	- 0.548 (0.294, 1.021)*	- 0.617 (0.327, 1.162)*	- 0.576 (0.306, 1.084)*	- 0.537 (0.293, 0.986)**
Smoking During Pregnancy No *(ref)* Yes	- 0.938 (0.494, 1.779)	X	X	X	X	X
Maternal Asthma No *(ref)* Yes	- 0.878 (0.331, 2.332)	X	X	X	X	X
Maternal Age <21 years 21-34 years*(ref)* >34 years	0.679 (0.231, 2.000) - 0.578 (0.237, 1.410)*	X	X	X	X	
Maternal Height *For every 10cm increase*	1.123 (1.004, 1.255)*	1.151 (1.023, 1.295)**	1.151 (1.023, 1.294)**	1.166 (1.035, 1.314)**	1.139 (0.984, 1.318)*	1.133 (1.011, 1.269)**
Pre-pregnancy BMI ≤18.5 kg/m^2 18.5-24.9 kg/m^2 *(ref)* 25.0-29.9 kg/m^2 >30.0 kg/m^2	0.569 (0.314, 1.030) - 0.416 (0.151, 1.144) 0.313 (0.104, 0.942)*	X	X	X	X	X

Preeclampsia No *(ref)* Preeclampsia	- 0.475 (0.110, 2.052)		X	X	X	X
Gestational Diabetes No *(ref)* Yes	- 1.173 (0.615, 2.237)*		X	X	X	X
Placental Previa No *(ref)* Yes	- 1.500 (0.415, 5.424)			- 1.590 (0.393, 6.437)[6]	- 2.045 (0.488, 8.574)[6]	X
Placental Abruption No *(ref)* Yes	- 0.592 (0.290, 1.212)*			X	X	X
Cord Complications None *(ref)* Cord around the neck or body, knot in the cord, prolapsed or lacerated cord Short, 2-vessel or velamentous cord	- 0.850 (0.439, 1.646) 6.603 (1.835, 23.755)*			- 0.780 (0.386, 1.576) 5.424 (1.439, 20.451)**	- 0.811 (0.407, 1.616) 5.298 (1.395, 20.128)**	X
Gestational Weight Gain <10lb at 30 weeks or <20 lbs at term Normal *(ref)* >40 lbs at term	1.278 (0.147, 11.131) - 0.799 (0.098, 6.502)				X	X
Birth Weight Category						

SGA AGA *(ref)* LGA	0.691 (0.262, 1.822) - 1.110 (0.410, 3.006)				X	X
Anaemia No *(ref)* Yes	- 0.849 (0.320, 2.253)				X	X
Placental Delivery Spontaneous *(ref)* Expressed or assisted Manual Retained	- 1.144 (0.129, 10.114) 0.659 (0.369, 1.176) 3.119 (1.077, 9.033)*				- 0.813 (0.087, 7.567)[6] 0.616 (0.324, 1.174)[6] 3.452 (1.095, 10.881)**	X

[1]-Baseline Factors; [2]-Baseline +Mid-Pregnancy Factors; [3]-Cord and Placental Complications; [4]-Late and Post-Pregnancy Factors; [5]-Only Factors with a significance level of $p<0.05$;[6]-Variable remains in model despite not reaching statistical significance for the specified level of the outcome because for the other level of the outcome it reaches statistical significance; *-Covariates with a significance level of $p<0.20$; **-Covariates with a significance level of $p<0.05$

P.6. Blocked Logistic Regression Model of Baseline and Pregnancy Factors Hypothesized to Influence a Placental Weight Ratio ≥90th Percentile in Infant Born at ≤32 Weeks

	Odds Ratio (95% Confidence Interval)					
		Blockwise Model Building at p<.20				***Restricted to p<.05***
Predictors	**Univariable**	**Model 1[1]**	**Model 2[2]**	**Model 3[3]**	**Model 4[4]**	**Final Model[5]**
Parity 0 ≥1	- 2.170 (1.128, 4.174)*	- 2.081 (1.006, 4.306)**	- 2.136 (1.026, 4.444)**	- 1.768 (0.848, 3.688)*	- 2.224 (1.060, 4.664)**	- 2.185 (1.084, 4.408)**
Smoking During Pregnancy No *(ref)* Yes	- 0.630 (0.271, 1.465)	X	X	X	X	X
Maternal Asthma No *(ref)* Yes	- 0.492 (0.114, 2.119)	X	X	X	X	X
Maternal Age <21 years 21-34 years*(ref)* >34 years	1.148 (0.381, 3.464) - 1.139 (0.476, 2.721)	X	X	X	X	X
Maternal Height *For every 10cm increase*	1.139 (0.993, 1.306)	1.119 (0.970, 1.290)*	1.120 (0.972, 1.291)*	1.104 (0.955, 1.275)*	1.139 (0.984, 1.318)*	1.125 (0.981, 1.290)*
Pre-pregnancy BMI ≤18.5 kg/m^2 18.5-24.9 kg/m^2 *(ref)* 25.0-29.9 kg/m^2 >30.0 kg/m^2	0.898 (0.427, 1.891) - 0.863 (0.292, 2.555) 0.814 (0.276, 2.403)	X	X	X	X	X

Preeclampsia No *(ref)* Preeclampsia	- 0.342 (0.045, 2.583)		X	X	X	X
Gestational Diabetes No *(ref)* Yes	- 1.397 (0.673, 2.902)		X	X	X	X
Placental Previa No *(ref)* Yes	- 3.919 (1.324, 11.601)*			- 3.944 (1.072, 14.507)**	- 3.333 (0.904, 12.285)**	X
Placental Abruption No *(ref)* Yes	- 1.678 (0.857, 3.285)*			X	X	X
Cord Complications None *(ref)* Cord around the neck or body, knot in the cord, prolapsed or lacerated cord Short, 2-vessel or velamentous cord	- 0.816 (0.376, 1.774) 3.661 (0.681, 19.674)			- 0.720 (0.307, 1.691)[6] 1.281 (0.116, 14.137)[6]	- 0.694 (0.290, 1.663)[6] 1.932 (0.176, 21.260)[6]	X
Gestational Weight Gain <10lb at 30 weeks or <20 lbs at term Normal *(ref)* >40 lbs at term	∞ (0, ∞) - 1.149 (0.140, 9.421)				X	X
Birth Weight Category					X	X

SGA	1.708 (0.742, 3.929)					
AGA *(ref)*	-					
LGA	0.343 (0.045, 2.603)					
Anaemia						
No *(ref)*	-				X	X
Yes	2.677 (1.187, 6.037)*					
Placental Delivery						
Spontaneous *(ref)*	-				-	
Expressed or assisted	0 (0, ∞)				0 (0, ∞)	X
Manual	2.156 (1.060, 4.383)*				1.432 (0.628, 3.267)	
Retained	4.159 (1.022, 16.931)*				2.204 (0.407, 11.937)	

[1]-Baseline Factors; [2]-Baseline +Mid-Pregnancy Factors; [3]-Cord and Placental Complications; [4]-Late and Post-Pregnancy Factors; [5]-Only Factors with a significance level of $p<0.05$;[6]-Variable remains in model despite not reaching statistical significance for the specified level of the outcome because for the other level of the outcome it reaches statistical significance; *-Covariates with a significance level of $p<0.20$; **-Covariates with a significance level of $p<0.05$

Appendix Q: Detailed Description of Missing Placental Weights

Overall, LGA infants had 22.03% missing, AGA infants had 22.71% missing, and SGA infants had 23.48% missing. Therefore, since the missingness is evenly distributed among categories it is speculated that the missingness was random. Furthermore, the distribution of missingness by gestational age category was as follows: in term infants 22.81% had missing placental weight, in infants born between 33 and 36 weeks gestation there was 25.50% missing, and in infants born at ≤32 weeks there was 9.85% missing for placental weight. It was proposed that placentas were not weighed in high risk pregnancies, but the missingness is less in extreme preterm and SGA babies, so that theory is not likely plausible. The missingness by hospital revealed differences between Victoria Hospital with 54.16% missing and, St. Joseph's with 0.38% missing placental weights. This discrepancy is due largely to the placental weight not being collected at Victoria Hospital for the first 2 and a half year of the study time period. Furthermore, the placental weights between the two hospitals revealed very close similarities. The mean placental weight at Victoria Hospital is 670g (S.D.=161.32) and 660g (S.D.=160.94) at St. Joseph's hospital. The 10^{th} and 90^{th} percentiles are 505g and 486g and 885g and 872g for Victoria and St. Joseph Hospital respectively. Therefore, the differences between the two hospitals are not substantial.

CURRICULM VITAE

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Education

M.Sc., Epidemiology and Biostatistics **2010-Present**
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Youth Hockey Injury Study, Hockey Canada and University of Ottawa, Ottawa, Ontario

Presentations

Placental Weight Ratio (PWR) Distribution Curves and Risk Factors for Atypical PWRs
Paul Harding Research Day **May 2012**
Department of Obstetrics and Gynaecology, Western University, London, Ontario

Placental Weight Ratio (PWR) Percentile Distribution Curves
London Health Research Day **March 2012**
Schulich School of Medicine and Dentistry, Western University, London, Ontario

Measures of Fetal Growth Restriction and Subsequent Risk
CIHR Canadian Student Health Research Forum **June 2011**
Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba

Increasing Incidence of Vulvar Cancer in Canada
University of Ottawa Student Epidemiology Conference **April 2010**
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Awards and Distinctions

• Graduate Thesis Research Awards Fund ($500) **2012**

• University of Western Ontario Schulich Graduate Scholarship ($7000 per year) **2010-2012**

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