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Maternal Health and Pregnancy Outcomes Among Hispanics

**Edith C. Kieffer, MPH, PhD
Department of Health Behavior and Health Education
School of Public Health, University of Michigan
1420 Washington Heights
Ann Arbor MI 48109-2029**

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**THE MATERNAL AND CHILD HEALTH RESEARCH PROGRAM
MATERNAL AND CHILD HEALTH BUREAU, HRSA, PHS, DHHS
PARKLAWN BUILDING
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857**

MATERNAL HEALTH AND PREGNANCY OUTCOMES AMONG HISPANICS

I. INTRODUCTION

A. Nature of the Research Problem

Low birth weight is rare among Hispanic infants, despite the substantial proportion of mothers who live in poverty and receive inadequate prenatal care.¹ Given the nation's focus on low birth weight as a major public health indicator of maternal and neonatal health, this "better outcome" has reduced health policy and program attention to Hispanic mothers and infants.^{2,3} However, obesity, impaired glucose tolerance and diabetes are common among Hispanic women of childbearing age.⁴⁻⁷ These conditions are associated with maternal labor and delivery complications, cesarean section, and diabetes after pregnancy, and with fetal overgrowth, birth injuries, obesity and metabolic abnormalities in subsequent life among gestationally exposed infants.⁸⁻¹⁵ While low birth weight is an indisputably serious problem, the possible contribution of maternal obesity, abnormal glucose tolerance and other metabolic abnormalities during pregnancy to the high average birth weights of Hispanic infants has not been systematically assessed, nor have the associated risks for adverse maternal and newborn pregnancy outcomes in this population.¹⁶

Populations with a high prevalence of central body obesity, abnormal glucose tolerance and other metabolic abnormalities during pregnancy, including Mexican-Americans and several immigrant populations, American Indians and Native Hawaiians have higher birth weights and a higher prevalence of large-for-gestational age (LGA) infants than expected given their sociodemographic and prenatal care use characteristics.^{1,17} Since fetal overgrowth secondary to intrauterine overnutrition does not reflect normal processes of growth and maturation, a greater incidence of maternal and newborn complications and metabolic abnormalities might be expected, along with subsequent risk for poor health maternal and infant health outcomes, in these populations.⁸⁻¹⁵

B. Purpose, scope and methods of the investigation

This prospective, longitudinal cohort study of Hispanic mother-infant pairs was designed to examine the extent and impact of maternal central body obesity, abnormal glucose tolerance, and other metabolic abnormalities among pregnant Hispanic women and their infants. It was expected that these characteristics would transcend other maternal risk factors and complications of pregnancy, resulting in higher birth weights and a greater incidence of LGA infants than would be predicted based on models of risk that do not include these measures. Further, it was expected that these anthropometric and metabolic characteristics would result in a greater incidence of adverse maternal and newborn outcomes than would be predicted given the birth weight distribution alone. The theoretical model is portrayed in Figure 1.

Specific aims

The specific aims of this study of a community-based population of pregnant Hispanic women and their newborn infants were:

AIM 1. describe the distribution and prevalence of factors that may influence fetal growth and adverse maternal and newborn outcomes. These factors include: central body

fat distribution, body mass index (BMI), glucose tolerance and other metabolic characteristics; patterns of pregnancy weight gain, maternal sociodemographic and family characteristics, cigarette smoking, other maternal health conditions and prenatal care therapies that may influence fetal growth;

AIM 2. describe the relationships among maternal anthropometric, BMI and metabolic measures; patterns of pregnancy weight gain, maternal sociodemographic and family characteristics, cigarette smoking, other maternal health conditions and prenatal care therapies;

AIM 3. describe the prevalence and distribution of several measures of birth weight, gestational age and adverse maternal and newborn outcomes;

AIM 4. estimate the impact of central body fat distribution, glucose tolerance and other metabolic characteristics during pregnancy on birth weight and gestational age outcomes, after accounting for prepregnancy BMI, pregnancy weight gain, sociodemographic and family characteristics, cigarette smoking, other maternal health conditions and prenatal care therapies. (corresponds to HO 1.0)

AIM 5. estimate the impact of central body fat distribution, glucose tolerance and other metabolic characteristics during pregnancy on the incidence of adverse maternal and neonatal outcomes, after accounting for prepregnancy BMI, pregnancy weight gain, sociodemographic and family characteristics, cigarette smoking, other maternal health conditions, prenatal care therapies and gestational duration. (corresponds to HO 2.0)

AIM 6. assess whether adding central body fat distribution, glucose tolerance and other metabolic characteristics and prenatal treatment variables will result in a better fitting model for predicting birth weight and gestational age outcomes than traditional models based on sociodemographic, medical risk and prenatal care use characteristics. (corresponds to HO 3.0)

II REVIEW OF THE LITERATURE

The Hispanic paradox. A "Hispanic paradox" has been described and has been the source of hypothesis generation and study.¹²⁻²⁸ Similar percentages of Mexican-American and white non-Hispanic infants have low birth weight despite lower socioeconomic status and inadequate prenatal care use among Mexican-Americans.^{1,16,23,26} Indeed the focus of most research associated with fetal growth among Hispanics has focused on exploring protective factors presumed to reduce their risk of low birth weight.^{23,24} Social, dietary and behavioral aspects of traditional Hispanic culture are presumed to buffer this population from the psychological and economic stresses of life in the United States, thereby protecting newborns from low birth weight.²⁰⁻²⁴ A study by Zambrana et.al. found that while the low birth weight percentage in her Los Angeles study population was similar to that of the Mexican-American population of Los Angeles overall (4.6% and 4.9% respectively), it was 2.6% among Mexican

immigrant mothers.²⁶ Similar findings by others have led to the inclusion of nativity status and level of acculturation in studies of low birth weight.^{20-22,25-28}

Acculturation, socioeconomic status, health behaviors and health among Hispanics.

The relationships between level of acculturation and health care use,^{16,25,26,29} health behavior,^{22,26,27,30} and several measures of health, including obesity,^{18,31} diabetes,^{5,31} and birth weight^{20,22,25-28} have been examined in studies of Hispanic populations. These studies demonstrate a generally consistent pattern in which acculturation to U.S. mainstream society is associated with increased use of health services and worsening health behavior, e.g. poorer diet, increased use of alcohol and tobacco. Obesity and diabetes generally increase in the first generation, and among moderately acculturated individuals, particularly those residing in predominantly Hispanic communities.³¹ The low birth weight studies generally find that less acculturated Hispanic women have heavier infants and lower risk of low birth weight than women with a greater U.S. cultural orientation. After accounting for acculturation level, the effects of socioeconomic status diminish or disappear.^{20,31} Though these studies have confirmed links between increased acculturation and behavioral risk factors associated with poor fetal growth, a direct effect of acculturation on birth weight has not been demonstrated.²⁶ Despite the literature demonstrating associations among acculturation, obesity and diabetes, and studies associating maternal weight, diabetes and birth weight, studies of the impact of acculturation on birth weight have not accounted for the potential impact of maternal weight and metabolic status on birth weight, as is proposed in our study. While sociocultural and behavioral lines of inquiry are important, the complex interplay of factors influencing birth weight must ultimately involve physiological processes.

Obesity and diabetes among Hispanics. An extensive literature documents high prevalence rates of obesity, insulin resistance and type 2 diabetes among Hispanic populations.^{4-7,31,32,33} Central body obesity is particularly common among Hispanics and strongly associated with diabetes risk.^{5,32} Immigrants and other populations undergoing changes in lifestyle, including diet and energy expenditure, frequently experience a transition from low to high prevalence rates of these conditions.^{5,31,33,34} In populations with a high prevalence of obesity and diabetes, including Hispanics, insulin resistance and impaired glucose tolerance coincides with childbearing for many women.^{5,6} These women may enter pregnancy with previously undetected type 2 diabetes or susceptible to development of gestational diabetes (GDM) as their ability to secrete insulin fails to overcome their higher levels of insulin resistance as pregnancy progresses.¹⁰

Maternal fuel metabolism. Pregnancy is analogous to tissue culture in that the placenta and fetus are incubated in a medium that is provided by the mother.³⁵ Placental hormones are associated with increased maternal insulin secretion, diminished insulin sensitivity, hyperinsulinemia and mild post-meal hyperglycemia.³⁶ These conditions appear to serve the purpose of increasing the flux of ingested nutrients from mother to fetus, thereby promoting fetal tissue growth.³⁶ Pederson first proposed an explanation for the pathophysiology of the infant of the diabetic mother which became known as the hyperglycemia-hyperinsulinemia hypothesis.^{37,38} In its simplest form, the hypothesis

proposes that maternal hyperglycemia results in fetal hyperglycemia that, in turn, causes fetal pancreatic hypersecretion of insulin and fetal hyperinsulinemia. Insulin serves as a growth factor and fetal hyperinsulinemia causes the hypertrophy of fetal tissue. With the recognition that the concentration of other nutrients are also elevated in the pregnant diabetic woman and her fetus, and that these nutrients can also stimulate hypersecretion of insulin, the Pederson hypothesis has been modified and widely accepted.^{2,39,40}

The interaction among placental and maternal hormones largely determine the availability of metabolic fuels in the maternal circulation.^{36,41} Both pregnancy and maternal glucose intolerance are characterized by increased plasma concentrations of glucose, free fatty acids and triglyceride.³⁶ Triglyceride levels are increased 1.5 to 2-fold by the 3rd trimester of pregnancy.³⁶ Glucagon, a hormone produced by the alpha cells in the pancreas, mobilizes glucose from liver glycogen and facilitates gluconeogenesis.³⁶ Fasting glucagon levels have been reported to be higher in the pregnant than the nonpregnant state and to increase over the course of pregnancy.³⁶

In the pregnant fasted state, blood glucose levels are lower than in the non-pregnant state. Fasting insulin levels are low but increase moderately during pregnancy, being most elevated in the 3rd trimester.⁴² Levels in obese women with gestational diabetes are even higher.⁴² The metabolic response to feeding in pregnancy is characterized by hyperglycemia, hyperinsulinemia and hypertriglyceridemia.³⁶ The degree of these abnormalities may be associated with human chorionic somatotropin levels (hCS), a glycoprotein produced by the placenta that is largely responsible for the maternal insulin resistance seen in later pregnancy.⁴¹ In late pregnancy, peak glucose values are obtained approximately 1 hour after an oral glucose load. The peak insulin value also occurs at about 60 minutes, synchronous with the glucose peak.³⁶ Even mildly diabetic women have distinctly abnormal alterations in every type of maternal fuel.⁴⁰ These metabolic fuels in the maternal circulation are transferred to the placenta by a variety of processes.
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Impact of maternal fuels on fetal growth. Significant correlations have been identified between birth weight and maternal levels of glucose, triglyceride, free fatty acids and amino acids.^{35-41,46,47} Knopp et.al. assessed plasma triglyceride levels among previously fasting women, 1 hour after a 50g oral glucose load.⁴⁶ In non-diabetic women, triglyceride level was a stronger predictor of birth weight ratio than screening glucose level and remained significant after adjustment for maternal weight and weight gain in pregnancy.⁴⁷ Similar findings were recently reported by Nolan et.al. in Australia. However, maternal glucose level remains the only one of these fuels to be assessed in routine prenatal screening.^{48,49} Maternal glucose and other fuels exist on a continuous gradient.⁵⁰ Glucose levels below the threshold for diagnosis of diabetes have also been associated with increased fetal growth, after controlling for maternal age and weight.^{8,9,11,50-51-53} The association between maternal glucose levels and birth weight is often strongest in non-diabetic women with an abnormal glucose screen, since stringent glucose control and reduction of the risk of high birth weight is a major goal of prenatal care for diabetic women.^{9,11,48,49,54}

Maternal weight and weight gain. Maternal obesity appears to intensify insulin resistance and related metabolic abnormalities that are already present in later pregnancy.³⁹ However, the range of metabolic abnormalities associated with insulin resistance persist in women with GDM when body mass index (BMI) is taken into account.⁵⁵ Obese women tend to gain less weight during pregnancy, as do women with GDM, which may be explained, in part, by greater prepregnancy weight among GDM mothers and by dietary restrictions associated with diabetes care in pregnancy.^{41,56-58}

Maternal central body fat distribution. Landon has suggested that the metabolic heterogeneity among obese women may be explained by variations in body fat distribution, which may serve as a marker for early development of glucose intolerance during pregnancy.⁵⁸ Despite the association between increased central body fat distribution, insulin resistance, and diabetes in non-pregnant individuals³², few studies have examined these associations during pregnancy.^{58,59} Landon et.al. studied the relationship between body fat distribution (upper versus lower body obesity) and metabolic characteristics (fasting insulin, glucagon, glucose, and c-peptide) in non-diabetic women.⁵⁸ Among women with the same BMI, upper body obese women (waist/hip ratio ≥ 9) had higher fasting levels of insulin, glucose and glucagon and reached maximum levels of fasting insulin and glucose intolerance earlier in pregnancy. This prolonged hyperglycemia could result in early stimulation of fetal hyperinsulinemia.^{14,35, 58} Recently, Branchtein et.al. found that increased waist/hip ratio to predicted decreased glucose tolerance, controlling for maternal age, BMI and other risk factors.⁵⁹

Impact of maternal body fat distribution, weight and weight gain on fetal growth. Maternal obesity is associated with heavier birth weights in infants of both diabetic and non-diabetic women. However, most studies of this association either do not consider maternal glucose tolerance or treat it as a dichotomous (diabetic, non-diabetic) confounder.⁶⁰⁻⁶⁴ However, GDM is associated with both lower weight gain and heavier birth weight.⁵⁶⁻⁵⁷ The estimated effects of prepregnancy weight and weight gain in pregnancy appear to attenuate but not fully explain the impact of glucose and other maternal fuels on birth weight^{47,51,53} Studies of maternal body fat distribution have not assessed its impact on fetal growth or other outcomes. These remain to be studied.

Maternal weight, metabolism and other maternal and newborn abnormalities. In non-diabetic women, obesity is associated with greater risk for complications of pregnancy, labor and delivery, including hypertension, diabetes, induced labor, cesarean section and wound infection.^{62,65} Naylor et.al. found increased likelihood of cesarean section among mothers with GDM despite normalized birth weights with treatment in this group, while women with untreated "borderline" GDM had higher birth weight infants as well as increased risk of cesarean section.⁶⁶ Increased glucose levels in both diabetic and non-diabetic women have been associated with the same maternal complications as among obese women, along with increased maternal risk of diabetes after pregnancy¹³ and increased neonatal risk of birth injuries, metabolic abnormalities and respiratory

difficulties.^{8-11,15} Vohr et.al. have also demonstrated increases in newborn body mass index, triceps skinfold thicknesses and blood pressure associated with maternal glucose level, in addition to the contributions of maternal prepregnancy weight and weight gain.⁹ Increased risk of congenital anomalies is associated with uncontrolled maternal hyperglycemia during organogenesis in early pregnancy.^{14,36,40} Given the high prevalence of diabetes risk factors and decreased access to, and use of, health services among Hispanic women of childbearing age, many may enter pregnancy with undetected type 2 diabetes. Recent studies have identified increased risk for neural tube defects among infants of obese women and Hispanics. The former controlled for diabetes status, but neither study measured maternal fuel metabolism.^{67,68}

Maternal anthropometry and metabolism in pregnancy among Hispanics. There have been few published studies of obesity, insulin resistance, diabetes, their treatment during pregnancy or their consequences in the Hispanic population.^{6,34,53,69,70} Hollingsworth described maternal sociodemographic, metabolic and weight characteristics and pregnancy outcomes in 83 gestational diabetic and 40 non-diabetic Mexican-American women served by the University of California, San Diego.⁶ The mean birth weights of infants born to obese diabetic and nondiabetic women were 3812g and 3813g, respectively. The infants of lean gestational diabetic mothers weighed 3517g at birth compared to 3368g among infants of lean non-diabetic mothers. The small sample size of this study precluded analysis of the relative impact of the metabolic and other maternal characteristics on pregnancy outcomes. Homko et.al. reported characteristics and outcomes among 36 Hispanic women with gestational diabetes but small sample size again precluded complex analysis.⁶⁹ Forsbach et.al described the prevalence of gestational diabetes in a prenatal clinic population of almost 800 in Monterrey, Mexico.⁷⁰ Twenty-three percent had an abnormal glucose screening test and 4.3% of the population was subsequently diagnosed with gestational diabetes. Among women with a normal glucose screen test, 7.3% had infants who weighed $\geq 4000\text{g}$ at birth, compared to 15.9% among those with an abnormal screen and a normal diagnostic test, and 16.7% among those with gestational diabetes. Green et.al. reported that a modest association between maternal BMI and birth weight but not screening glucose level after the effect of maternal BMI was controlled, among Hispanic women in San Francisco.⁵³ This study did not account for the possible effects of treatment for diabetes among the women with higher glucose levels. *In summary, despite increased risk for obesity, insulin resistance and diabetes among Hispanic women of childbearing age, very little is known about the impact of these conditions on fetal growth, birth weight, or adverse maternal and newborn outcomes.*

Cigarette smoking and fetal growth. Prenatal smoking is a major cause of fetal growth retardation in both obese and non-obese women.^{70,71} It has been suggested that the vasoconstricting effect of smoking may have a smaller impact on fetal growth in obese than lean women, due to the offsetting effects of increased blood and glucose supply in heavier women.⁶⁵ The combination of low pregnancy weight gain and smoking appears to have the greatest negative impact on fetal growth in both obese and non-obese women.⁷²

Other maternal conditions influencing fetal growth. Hypertensive disorders, whether preexisting or arising during pregnancy, may result in uteroplacental insufficiency, decreased blood flow to the uterus, fetal hypoxia and growth retardation.⁷³ Ananth et.al. documented increased risk of growth retardation in the newborns of both black and white mothers, whether hypertension was chronic or pregnancy-induced, with or without eclampsia. Reduced risk of large-for-gestational age (LGA) was associated with pregnancy-induced hypertension in white mothers and eclampsia in both races.

Anemia during pregnancy has also been associated with fetal growth restriction though the degree of direct causality is still a matter of debate.⁷⁴ Whether anemia causes lowered birth weight or is a marker for maternal malnutrition, failure of red blood cell mass to increase, low consumption of energy and other nutrients, or other problems, several studies have found increased risk of low birth weight in anemic mothers.^{75,76} Inadequate weight gain and anemia are correlated, though causality is again unknown.⁷⁴

Prenatal care. Because of the association between higher pregnancy weight gain and decreased risk of low birth weight, mothers are usually counseled about recommended weight gain upon entry to prenatal care.^{77,78} Screening for gestational diabetes is recommended for the beginning of the 3rd trimester since diet, exercise or insulin treatment may reduce adverse maternal and infant outcomes.^{41,48,49,79-82} Anemia and hypertension may also be identified and treated during pregnancy.^{77,78} These treatments have the potential to reduce either reduce or increase fetal growth depending on the underlying problem. However access to, and the success of prenatal treatments, are influenced by the timing of entry to prenatal care as well as the services provided. Late entry to prenatal care is common among Hispanic women^{16,37} which could influence birth weight-related outcomes in either direction depending on the prevalence, severity and impact of the hypothesized predictors of fetal growth and other outcomes in this population.

III. STUDY DESIGN AND METHODS

A. Study Design

A.1.1 Type of study. This was a prospective cohort study.

A.1.2. Strengths and limitations of the design chosen.

A prospective design was necessary since measures of body fat distribution and metabolism (other than glucose) are not routinely collected during prenatal care. The expanded data set allowed us to assess the relationship between maternal body fat distribution, metabolism and other maternal characteristics and health conditions associated with fetal growth. In addition to a description of the distribution of anthropometric and metabolic characteristics in the population, prevalence estimates of

overweight and obesity and chronic hypertension, and the incidence of gestational diabetes and hypertension, anemia, newborn macrosomia, preterm birth and adverse maternal and neonatal outcomes in a community-based population of Hispanic women and their newborn infants are available. Analyses of study hypotheses are conducted in a community population that includes women with all levels of risk rather than in a hospital-based population. Loss to follow-up of women who were recruited into the study is a disadvantage of the prospective design.

Clinicians were not blinded to results of maternal glucose tests. Therefore, all women with abnormal results according to NDDG criteria⁹² were referred to the Henry Ford Hospital Endocrinology Clinic for treatment (insulin and/or diet). We chose to focus resources on measures of body fat distribution and other maternal fuels that we hypothesized contribute to fetal overgrowth beyond that explained by maternal glucose levels. These measures have not been frequently studied or reported in non-diabetic (particularly Hispanic) women and may be less susceptible to treatment effects

B. Population Studied

B.1 Population description.

The majority of Detroit's Hispanic populations resides in Southwest Detroit, which is the most ethnically diverse part of the city. The Hispanic population of southwest Detroit was estimated to be approximately 40,000 in the 2000 U.S. Census, although this is believed to a substantial undercount due to the large number of undocumented persons. Almost 90% of the Hispanic population is of Mexican descent and many are very recent immigrants. The community grew rapidly during the study period. A large percentage of community residents live below the poverty line and unemployment rates are high. More than 50% of Southwest Detroit adults have not graduated from high school.

The Community Health and Social Services (CHASS) Center, Inc. is a federally qualified health center that is located in southwest Detroit. It was established in 1970 as a community-based organization devoted to providing health care, social, and other services to under-served residents of southwest Detroit. Most CHASS patients are Hispanic, drawn by the large bilingual, bicultural staff and trusted place in the community. Most CHASS patients are uninsured and have incomes below the poverty line. Care is provided regardless of income or insurance status.

A large majority of Hispanic women from the southwest Detroit community chooses to receive their prenatal care at CHASS. By contractual arrangement, prenatal and obstetric care, including high risk and tertiary care, are provided in association with Henry Ford Hospital in Detroit. Except in some emergencies, all CHASS patients deliver their infants at Henry Ford Hospital and almost all Hispanic women who deliver at Henry Ford receive their prenatal care at CHASS. To the extent possible, all pregnant Hispanic women who sought care at CHASS within the two-year study period were recruited to participate in the study.

C. Sample Selection

A total of 1346 Hispanic women entered prenatal care at CHASS between Jan 5, 1999 and February 28, 2001. Figure 1 outlines the participation status of these women. Excluded from eligibility were 9 twin pregnancies and 39 pregnancies where mothers had already participated during the study period during a previous pregnancy, leaving an eligible cohort of 1298 pregnant women. The study was unable to obtain consent from 110 (8.5%) of these women. Less than 4% (n=49) were adult women who remained in care at CHASS but failed to consent. There were 39 women under the age of 18 who could not participate because staff were unable to obtain permission from parents who often did not live in the area. Three women miscarried before consent could be obtained, thirteen women transferred care soon after their pregnancy was diagnosed, and 6 women were excluded due to very late entry to care. Of the 1188 women who consented to participate in the study, 140, (11.8%) did not have a recorded birth at the study hospital. These 140 included 20 pregnancies that ended in miscarriage, 59 women who transferred their care elsewhere, 34 who dropped out of care at CHASS without officially transferring care, and 49 women who completed care at CHASS, but for whom no birth is recorded at the study hospital. Exclusions leave 1041 mother-baby pairs eligible for analysis.

There were several significant differences between mothers who did not consent and those who consented to participate in the study (Tables 1a and 1b) Women who did not consent were much more likely to be less than 18 years of age (35% compared to 3-4% of consenting women). This characteristic likely influenced the others. A significantly higher percentage of non-consenting mothers were U.S. born, unmarried, and primiparous. These women were significantly less likely to be obese, although this difference was not evident after age adjustment, and had somewhat lower hemoglobin levels. In addition, non-consenting women were more likely to have late entry to care which made it less likely that we could gain consent early enough in gestation to collect the needed anthropometric data.

D. Instruments

D.1 Data Collection

Data sources included CHASS and Henry Ford Health System medical records and electronic information systems, which were abstracted by study staff; interviews and anthropometry conducted longitudinally during pregnancy by study staff, and assays conducted by the University of Michigan on blood drawn and handled according to study protocols by CHASS laboratory personnel. Copies of the abstraction forms and manuals of procedure are located in the Appendix. Changes in CHASS clinic protocol forced the elimination of some of the intended variables (e.g. health insurance, income, paternal education, prenatal nutrition therapies) due to large amounts of missing data.

Independent variables

D.1.1 Sociodemographic, family and health history data. These data include family (mother, father, sister, brother) history of diabetes, maternal age, parity (coded for most analyses as multiparous, yes or no), marital status, ethnicity, acculturation, and maternal educational. During the first prenatal visit, CHASS nurses obtain and record maternal and family health history (including family history of diabetes); menstrual and obstetric history, LMP and medical complications since the LMP. Maternal and family socio-demographic data were obtained by CHASS social workers during the first prenatal visit. Additional sociodemographic data, smoking and alcohol consumption, physical activity and social support were obtained by interviews conducted by study staff at the first prenatal visit and at 26 weeks. Acculturation variables included birth inside or outside of the U.S., duration of residence in the U.S. in a Latino community, primary language, childhood in rural versus urban environment.

D.1.2 Gestational Age and Ultrasound data. An initial ultrasound assessment was obtained for all pregnant women at Henry Ford Hospital immediately after the first prenatal visit. Measures of biparietal diameter, femur length, abdominal and head circumference and the estimated gestational age associated with each measure were recorded. Gestational age was established primarily by using ultrasound criteria, which were available almost universally for CHASS patients. The variability of the single biparietal (BPD) widens as gestation progresses for ± 7 days at <14 weeks gestation, to ± 21 days at 29-40 weeks gestation. Using paired BPD's, the gestational age can be calculated with a variability of ± 7 days. When the LMP date falls within the confidence limits of the ultrasound BPD and femur length (FL), the role of ultrasound was to confirm the LMP. When the LMP fell outside of the confidence limits of the ultrasound BPD and FL date, the ultrasound date was used. All gestational ages were assigned by review of available data by a single perinatologist who was blind to the glucose and birth outcome status of the mother-infant pair.

D.1.3 Maternal weight, height, and blood pressure. Maternal self-reported prepregnancy weight, actual weight, height, and blood pressure were recorded at the positive pregnancy test confirmation visit, which obstetric patients experience at CHASS at an average of 6-12 weeks gestation. Maternal weight and blood pressure measurements were subsequently obtained at each prenatal visit. Height and weight were measured using a standard calibrated beam balance scale. Blood pressure was obtained using a standard sphygmomanometer. Prepregnancy body mass index (BMI) ($\text{weight}[\text{kg}]/\text{height}[\text{m}]^2$) was also coded into IOM recommended categories: underweight (<19.8), normal weight (19.8-26.0), overweight (>26.0-29.0) and obese (>29.0).⁷⁷ In cases where prepregnancy weight was unknown or missing, a proxy called predicted prepregnancy weight, was used for mothers with a first prenatal visit weight obtained within the first 10 weeks of pregnancy, following procedures described by Siega-Riz.⁶³

D.1.4 Maternal anthropometry. Anthropometric and skinfold measurements were obtained at the first physician visit, and again at the time of metabolic testing at 28 weeks. Body circumferences were measured to the nearest 0.5 cm with a flexible metric tape at three sites: waist, hip (gluteal area), and upper arm. Waist circumference was

measured at the narrowest horizontal circumference in the area between the ribs and iliac crest. Hip (gluteal area) circumference was measured at the level of maximal extension of the buttocks posteriorly. Arm circumference was measured at the mid-point of the upper arm. Triceps skinfold thickness was measured to the nearest millimeter using a Lange skinfold caliper at the triceps at the same level where the arm circumference was obtained.

Measures of central body fat distribution included two anthropometric measures: waist circumference and waist/hip ratio (circumference of the waist/circumference of the hip). Individuals with high central body fat distribution were defined as having a waist-hip ratio of ≥ 0.9 .

D.1.5 Prepregnancy weight gain was calculated by subtracting prepregnancy weight from the last weight recorded during prenatal care if the last visit occurred within 7 days of delivery. Women without prepregnancy weight (reported or predicted) or with a last weight recorded prior to 7 days before delivery were excluded from analyses of gestational weight gain. Weight gain was also categorized as below, at, or above the IOM weight gain recommendations that are based on prepregnancy BMI category.

D.1.6. Metabolic measures and other laboratory tests. At the first prenatal visit, technicians obtained whole blood for analysis of random blood glucose, hemoglobin and hematocrit; VDRL, HIV, rubella, hepatitis surface antigen, blood type and Coombs. Urinalysis and cultures were done to identify urogenital tract infections; a cervical culture for gonorrhea is done using agar modified Thayer Martin media. An endocervical culture for chlamydia was conducted using GEN-PROBE (DNA probe) Amplified Systems.

Women with random glucose levels over 125 mg/dl were scheduled immediately for a 1 hour oral 50 gram glucose screening test, which is conducted at CHASS after an overnight fast. Women with screening test results ≥ 130 mg/dl were immediately scheduled for an OGTT. Those with levels < 130 mg/dl and those with normal OGTT results are tested again, along with all other pregnant women at 26 weeks gestation, using the same procedures and criteria. The diagnosis of diabetes was made by the CHASS medical director, using National Diabetes Data Group (NDDG) criteria, i.e. 2 or more glucose values \geq : 105mg/dl at fasting, 190 at 1 hour, 165 at 2 hours, and 145 at 3 hours. Women with diabetes are referred for diabetes management to the Endocrinology Department of Henry Ford Hospital.

All women undergoing the OGTT had blood drawn assayed for glucose, insulin, and free fatty acids and plasma for glucagon. In the glucose fed state (1 hour after a 50g oral glucose load) we assessed levels of insulin and glucose (measures of insulin sensitivity and insulin resistance), and triglycerides. In the post-absorptive (fasting) state, we measured levels of insulin, glucagon, and glucose and total free fatty acids to assess maternal fuel homeostasis.

Mediating or confounding variables

D.1.7 Cigarette smoking. Measures of tobacco use were assessed by interview and questions were based on those used in the Hispanic Health and Nutrition Survey (HHANES).⁸⁹⁸³

D.1.8 Maternal health conditions. Data were collected on anemia and hypertensive disorders during pregnancy. Anemia was defined as a hemoglobin of ≤ 11.0 in the 1st or 3rd trimester and/or ≤ 10.5 in 2nd trimester; or a hematocrit of $\leq 33\%$ in the 1st or third trimester and/or $\leq 32\%$ in 2nd trimester.⁷⁷ Hemoglobin status during pregnancy was also assessed using hemoglobin Z scores, based on the hemoglobin level at the first prenatal visit using methods described by Scanlon et al.⁸⁴ Maternal hemoglobin was adjusted for maternal smoking using the adjustment factor of +0.3. Hemoglobin Z score then calculated using a gestational-age-specific hemoglobin reference value as: [Hemoglobin Z score = (Measured hemoglobin adjusted for smoking status) reference median hemoglobin for gestational week of measurement) / SD of reference hemoglobin distribution]. Diagnoses of hypertensive disorders are recorded by CHASS and Henry Ford physicians during the antepartum, intrapartum, and postpartum periods. In addition, blood pressures were obtained at each prenatal visit.

D.1.9 Prenatal care therapies. Changes in the clinical protocol and staffing at CHASS during the study period, including the loss of the Clinic registered dietician, reduced the proportion of participants who received professional nutrition counseling, preventing use of these variables. Adequacy of prenatal care was based on an index (the revised GINDEX) that includes the trimester prenatal care began and the number of prenatal care visits, given the gestational age of the infant at birth. Prenatal care adequacy was first defined as a scale between 1 and 4 with 0 = intensive, 1 = adequate, 2 = intermediate, and 4 = inadequate. Since the birth outcomes of the very few women who received intensive levels of care were similar to those with adequate care, this variable was finally coded as adequate (yes or no).

Outcome variables

D.1.10 Maternal and infant outcome data. Intrapartum and postpartum processes and outcomes, were abstracted from CHASS and Henry Ford Hospital records after delivery. **Infant birth weight** was measured in grams within an hour of birth on a Detecto recumbent scale. **Gestational age** as defined above was also used as an outcome variable.

The study collected information about certain maternal complications of pregnancy, complications of labor and delivery, maternal postpartum complications, and certain adverse results in infants.

Adverse maternal outcomes included antepartum outcomes: polyhydramnios, urinary tract infection, preeclampsia; intrapartum: prolonged (>2.5 hours) 2nd stage labor, premature rupture of membranes, secondary arrest of dilatation, 3rd or 4th degree perineal lacerations, vaginal or cervical laceration, preeclampsia (hypertension plus proteinuria of 300 mg from a 24 hours urine collection) and eclampsia (preeclampsia plus

seizures and/or coma); manual rotation, forceps or vacuum extraction in a vaginal delivery, and cesarean section (repeat and primary); and number of hospital days

Adverse neonatal outcomes included: Apgar <7 at 5 minutes, asphyxia, resuscitation needed: oxygen with bag and mask, endotracheal tube, external cardiac massage, umbilical catheter; respiratory problems: meconium aspiration, transient tachypnea of the newborn, respiratory distress syndrome (RDS) and persistent pulmonary hypertension; birth injuries: hematoma, lacerations, fractures and nerve injuries; sepsis: suspected sepsis (risk factors and/or symptoms of infection treated with ≥ 3 days of antibiotics but with negative blood cultures) and proven sepsis (blood culture positive and infant treated with full course of antibiotics); metabolic abnormalities: polycythemia (venous hematocrit >70%), hyperbilirubinemia (serum bilirubin levels of >12 mg/dl in formula-fed infants and >14 in breastfed infants) and hypoglycemia (glucose levels <30 mg/dl); congenital anomalies: ventricular septal defect, transposition of the great arteries, other cardiac (not heart murmurs), neural tube defects, spinal agenesis-caudal regression syndrome, left micro colon syndrome, and number of infant hospital days.

Although an attempt was made to abstract details on a large number of potential outcome variables, outcomes with fewer than 10 events in the study sample were not considered for initial analysis. Included among these outcomes with larger prevalences were the premature rupture of membranes, perineal lacerations, induced labor, Cesarean section, infant respiratory problems, infant metabolic problems, use of resuscitation, and sepsis. In addition we analyzed relationships with the number of days the mother and infant were hospitalized

E. STATISTICAL ANALYSES

Descriptive statistics were obtained for all variables using mean and standard deviation for continuous variables, and frequencies and proportions for categorical variables.

Maternal demographic, biological anthropometric and metabolic characteristics by glucose level and gestational diabetes status were assessed with one way analysis of variance using general linear models (GLM) for equal variances and Welch's ANOVA for unequal variances. The equality of variances was tested with Levene's F statistic. Differences within groups were assessed with post hoc pairwise comparison analysis using Tukey multiple comparison procedure.

Bivariate and multivariate linear regression analyses were performed to assess the relationships between sociodemographic, biological anthropometric and metabolic characteristics as independent variables and birth weight adjusted for gestational age as dependent outcome variable. The normality and linearity assumptions of linear regression models were assessed by univariate analyses and by categorizing each continuous variable into multiple dichotomous variables. Interaction terms between independent variables were also considered. None of the interaction effects was statistically significant. The coefficient of determination (R^2) was used as a quantitative

measure of how well the independent variables explain the outcome. For the multiple linear regression models, adjusted R^2 was used to control for the number of independent variables in the equation.

Pearson correlation analysis and partial correlation analysis were performed to assess the strength of the relationship between the outcome variable (birth weight adjusted for gestational age) and the independent variables in the linear regression models. Stepwise selection procedure was used to select the best possible model.

Bivariate and multivariate logistic regression analyses were performed to assess the relationships between sociodemographic, biological anthropometric and metabolic characteristics as independent variables and large for gestational age (LGA), small for gestational age (SGA), and pre-term as dependent outcome variables. The linearity assumption for logistic regression models was assessed by categorizing each continuous variable into multiple dichotomous variables of equal units and plotting each variable's coefficient against the midpoint of the variable. We also performed the Mantel-Haenszel chi-square test for trend. Multicollinearity was assessed using the Pearson correlation coefficient statistic. Accuracy, reliability, and precision of regression coefficients were assessed by calculating the number of events per variable (EPV), the ratio of the number of outcome events to the number of predictor variables. An EPV of at least 10 indicates that the estimates of regression coefficients and their confidence intervals are reliable. The possible interactions among variables were assessed using the Breslow and Day χ^2 test. The -2 Log Likelihood Ratio test was used to test the overall significance of the logistic regression models. The significance of the variables in the models was assessed by the Wald χ^2 test, odds ratios (ORs) and 95% confidence intervals (CIs). The fit of the model was assessed by the Hosmer-Lemeshow goodness of fit χ^2 test. To assess outliers and detect extreme points in the design space, logistic regression diagnostics were performed by plotting the diagnostic statistic against the observation number using hat matrix diagonal, and Pearson and Deviance residuals analyses.

A p-value < 0.05 was defined as the level of statistical significance. All statistical analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC).

IV. PRESENTATION OF FINDINGS

AIM 1. describe the distribution and prevalence of factors that may influence fetal growth and adverse maternal and newborn outcomes.

Sociodemographic characteristics

The sociodemographic characteristics of the study population are summarized in table 2a. The average age of the women was 25.2 years. The largest percentage (36.5%) of women was in the 20-24 age group; 15.9% were less than age 20, including the 5% who were less than 18 years of age. Seventeen % of the women were over age 29. Almost 60% of the women were multiparous, including 3.7% with 4 or more children. Fifty-four percent of the women reported being married.

Only 8% of participants were born in the U.S. More than 90% of the women were of Mexican, and 3% of Puerto Rican, ancestry. The remaining women were from various Latin American countries. The ancestry and nativity of husbands/partners and parents were almost identical, although the percentage of U.S.-born parents were even smaller. Participants had lived in the U.S. an average of 4.6 years, with 13.5 % living in the U.S. for less than one year and 64.2% for less than five years. The average age at arrival in the U.S. was 20.4 years. Almost half (48%) of the women had lived in rural areas of their native countries prior to age 16. Less than 1% of women spoke only English, 23% reported that they spoke Spanish and English equally and 77% spoke only Spanish. However, the latter percentage is believed to be higher since most women who said they spoke both had difficulty conducting their interviews in English and switched to Spanish.

Approximately 85% of the women last attended school outside of the U.S. This group averaged 3.73 years of education, with 90% having less than 9 years of education and 1.7% having more 12 years of education. Among the women last educated in the U.S., the mean numbers of years of education was, with 37.9% having less than 9 years of education and 34.5% having more 12 years of education.

Prenatal care and health history

Study participants entered prenatal care at an average of 17.4 weeks of gestation and had an average of 9.5 visits (Table 2b). The largest percentage (71%) began care in the second trimester. Less than 2% received intensive levels of prenatal care. Eleven percent of women were classified as having adequate prenatal care, primarily due to infrequent initiation of care in the first trimester (15.9%). An intermediate level of care was received by 73% of women and 14% received an inadequate level of prenatal care. A family history of diabetes or hypertension was reported by approximately 19% and 22% of women, respectively. Among multiparous women, a history of gestational diabetes or gestational hypertension was reported by 5.4% and 6.4%, respectively.

Behavior

Smoking

Smoking before pregnancy was reported by 8.6% of women, with only 1.8% reporting continued smoking after becoming pregnant.

Alcohol consumption

Approximately 2 % of women (n=17) reported consuming any alcohol during pregnancy.

Physical Activity

Almost 75% of women reported fewer than 4 periods of moderate physical activity per week; 13.5% reported 4-6 periods per week and 11.0% reported this level of activity at least 7 times per week. Even when work and recreational activity were combined, almost 70% of women reported doing little or no exercise during pregnancy. Only 4.5% of women reported high levels of physical activity.

Anthropometry (Table 3a)

Pregravid weight

On average, participating women weighed 139.4 pounds before they became pregnant and were 156.3 cm (5 feet and 1.5 inches tall) (Table 3a). The average pre-pregnancy BMI of study participants was 25.9 kg/m². According to the IOM categories for classifying women during pregnancy, 6.7% of women were underweight, 51.6% were normal weight, 18.1% were overweight and 23.7% were obese before they became pregnant.

Weight gain during pregnancy

The mean pregnancy weight gain among study participants was 12.9 kgs (or 28.4 pounds). Using the IOM weight gain recommendation categories, 46.9% of women gained less weight than recommended for their BMI category, while 36.2% gained more than recommended. Among women who were underweight before pregnancy, 27.7% gained less, and 30.8% gained more than recommended. Among women with normal pregravid weight, 66.0% gained less than recommended and 31% gained more than recommended. Among overweight women 19.2% gained less than recommended and 51.2% gained more than recommended. Among obese women, the IOM did not define an upper weight gain limit. If the recommendations for overweight women are applied for obese women, 32.4% of these women gained less than recommended, while 37.9% gained more than recommended; a percentage that could be considered conservative.

Waist, hip and arm measurements

Among the 986 women who had their first waist measurement prior to 26 weeks gestation, the mean waist circumference was 90.7 cm, hip circumference was 102.8 cm, for an average waist-to-hip ratio of 0.88. Thirty-six percent of women had a waist-to-hip ratio of greater than 0.9. Mean upper arm circumference and triceps skinfold measurements were 28.2 cm and 27.2 mm, respectively. The mean upper arm fat area (UAFA) was 44cm²

Metabolic characteristics (Table 3b)

Glucose, insulin, cholesterol and triglyceride levels at the 1 hour 50 gram glucose screen test

The mean glucose level derived from the 50g glucose screen test was 116.2 mg/dL. When screen glucose values were divided by category, 29.1% had values less than 100 mg/dL and 27.1% had values greater than 130 mg/dL. The latter group were considered to have an abnormal glucose screen and referred for an OGTT. Among these women, 13.7% (3.3% of the entire study population) had 1 abnormal OGTT value and 26.1% (6.3% of the study population) had 2 or more abnormal values. The mean insulin level at the time of the glucose screen test was 95.5 uU/mL, for a mean insulin to glucose ratio of 0.81. The mean total cholesterol level was 223.1 mg/dL, including a mean HDL of 63.6 mg/dL. The mean triglyceride level was 214.1 mg/dL.

Health conditions during pregnancy

Gestational diabetes (GDM) and hypertensive disorders of pregnancy

No participants reported that they had diabetes (either type 1 or type 2) or chronic hypertension prior to pregnancy. Overall, 6.8% of the participants were diagnosed with gestational diabetes during this pregnancy. Only eight women were diagnosed with a hypertensive disorder during this pregnancy.

Hemoglobin levels and anemia (Table 3c)

Seven percent of the women were anemic at entry to prenatal care as defined by the IOM trimester-specific IOM criteria for anemia. These included 3%, 5% and 15% of women who entered care in the first, second and third trimesters, respectively. All women were placed on iron supplements at entry to care. If anemia is defined by very low or low trimester-specific z-scores for hemoglobin, the percentage of anemic women was 2% overall, and <1%, 1% and 7%, for women that entered care in the first, second and third trimester, respectively.) High and very high hemoglobin was found for 4% of women in this study, including 5%, 5% and 2% in the first, second and third trimesters, respectively.

AIM 2. describe the relationships among maternal characteristics and glucose

The bivariate relationship between selected maternal characteristics and screening glucose level was examined (Tables 6a and 6b). As expected, there was a significant linear increase in maternal glucose level as maternal age increased; $p < 0.001$. Among women without GDM, mean age increased from 23.3 years for women with glucose levels under 100 mg/dL to 26.7 for women with glucose levels over 129; $p < 0.001$. Women with GDM were 28.6 years of age on average. The percentage of women with a family history of diabetes increased significantly with increasing glucose level; $p < 0.001$. Among women without GDM, the percentage with a family history of diabetes increased from 12.0% of women with glucose values less than 100 mg/dL to 23.3% of women with glucose values greater than 129 mg/dL; ($p < 0.001$), and to 26.5% of women with GDM. There was no significant relationship between maternal education in years, marital status, multiparity, number of prenatal visits, history of a hypertensive disorder or anemia with increasing maternal glucose level.

There were significant linear relationships between some anthropometric, and most metabolic, variables and glucose level. Among women without GDM, the mean BMI increased from 24.8 among women with glucose values less than 100 mg/dL to 26.6 among women with glucose values greater than 129 mg/dL; ($p < 0.001$), and to 28.4% of women with GDM. Waist-to-hip ratio increased from 0.87 to 0.89 among women in the lowest to highest glucose category, among women without GDM; $p < 0.001$, and to 0.91 among women with GDM. However, pregnancy weight gain was highest among women with normal glucose levels (100-129mg/dL), perhaps due to diet and weight gain cautions for women with abnormal glucose screen values or GDM.

Insulin values increased steeply and significantly with each increase in glucose category ranging from 64.8 uU/mL among women with glucose values less than 100 mg/dL to 129.3 uU/mL among women with glucose values greater than 129 mg/dL; ($p < 0.001$); and to 144.4 uU/mL among women with GDM. Insulin-to-glucose ratios followed a similar pattern, ranging from 0.74 to 0.88 among women without GDM, and to 0.89 among women with GDM; $p < 0.01$. Among women without GDM, triglyceride values increased from 200.8 mg/dL among women with glucose values less than 100 mg/dL to 219.4 mg/dL among women with glucose values greater than 129 mg/dL; ($p < 0.001$), and to 247.6 mg/dL among women with GDM. HDL values were inversely, but not significantly related to glucose levels declining from 64.9 mg/dL among women with

glucose values less than 100 mg/dL to 63.8 mg/dL among women with glucose values greater than 129 mg/dL; $p < 0.64$. However, women with GDM had significantly lower HDL values of 57.9 mg/dL; $p < 0.01$.

AIM 3. describe the prevalence and distribution of several measures of birth weight, gestational age and adverse maternal and newborn outcomes

Birth weight and gestational age (Table 4a)

The mean birth weight of infants born to study participants was 3408 grams. Only 3.6% of infants were born weight less than 2500 grams, including 0.5% who were very low birth weight (less than 1500 grams) and 3.1% who were moderately low birth weight (1500-2499 grams). Almost 9% of infants weighed more than 4000 grams at birth.

The average gestational age of study infants was 39.3 weeks. Only 7.7% of infants were born preterm (less than 37 completed weeks of gestation), including 1.3% who were very preterm (less than 33 completed weeks of gestation). Only 4.5% of infants were SGA, while 9.3% were LGA.

Other adverse maternal and infant outcomes

Table 4b presents selected maternal and infant adverse outcome prevalence and incidence data. The most frequently reported maternal adverse outcomes were induced labor (10.5%) and cesarean section (18.35%). In addition, the mean number of maternal hospital days was 1.6 days (0.9). The mean number of hospital days for infants was higher at 2.2 days (6.0). The most frequent adverse event among infants was the need for resuscitation (33.2%) and prevalence of infant metabolic abnormalities (hyperbilirubinemia and hypoglycemia) at 7.8%. In addition, there were 41 cases of respiratory problems (3.9%).

Bivariate relationships between maternal characteristics and birth weight outcomes

Table 5 presents the variables with at least one significant relationship with a birth weight outcome variable.

Sociodemographic variables

Only age ($p = 0.001$) and multiparity ($p = 0.0001$) were associated with increasing birth weight, adjusted for gestational age. Increasing maternal age was also associated with slightly reduced risk of preterm birth (OR: 0.94; CI: 0.89-0.99.) However, age was not significantly associated with LGA or SGA. Multiparity reduced the odds of preterm birth by 23% (CI: 0.59-0.99), increased the risk of LGA by 21% (IC: 1.03-1.42) but was not significantly associated with SGA. There was no significant relationship between marital status, maternal education, ethnicity or any measure of acculturation with birth weight, LGA, SGA or preterm birth.

Prenatal Care Use

Adequate prenatal care was a significant risk factor for preterm birth (OR: 2.91; CI: 1.63-5.18) and was marginally associated with mean birth weight (PE: 77.9; $p = 0.06$), but not with LGA or SGA.

Behavior

There were inadequate numbers of women who smoked or drank alcohol during pregnancy to test associations. Physical activity was not significantly associated with birth weight.

Family History of diabetes

There was no association between family history of diabetes and any of the birth weight outcomes.

Hemoglobin Z-Scores

There was no significant effect of trimester-specific hemoglobin Z-score on mean birth weight adjusted for gestational age, although the direction of effect in each trimester was to reduce birth weight. There were inadequate numbers of LGA, SGA and preterm births to assess the effect of hemoglobin z-score on these outcomes.

Anthropometric variables

Significant relationships were found between most anthropometric variables and birth weight variables. Three variables (hip circumference, triceps skinfold and upper arm circumference) were associated with all three birth weight outcomes. Increases in upper arm circumference (PE: 24.1; p=0.0001); BMI (PE: 13.2; p=0.0001); triceps skinfold (PE: 10.3; p=0.0001); hip circumference (PE=9.08; p=0.0001); weight gain (PE: 8.22; p=0.0002) and upper arm fatness (PE: 1.08; p=0.006) were each significantly associated with increased birth weight. Increased BMI, hip, triceps and upper arm circumference each increased the odds of LGA and decreased the risk of SGA. Increasing weight gain also decreased the risk of SGA, while increased upper arm fatness slightly increased the risk of LGA. Waist-to-hip ratio (whether measured as a mean or percentage >0.09) was not a significant predictor of birth weight, LGA or SGA, whether measured as a mean. No anthropometric variable was associated with preterm birth.

Metabolic variables

In bivariate regression analyses, glucose level at the 1 hour glucose screen test was the only metabolic variable that was significantly associated with birth weight, with each 10 mg/dL increase in glucose value associated with a 19.3 gram increase in birth weight, adjusted for gestational age. Increased glucose level at the screen was also associated with increased risk of LGA but was not associated with changes in risk of SGA. Higher triglyceride levels at the screen test increased the odds of LGA but were not associated with SGA. Insulin, insulin to glucose ratio, cholesterol and HDL levels at the screen were not associated with any birth weight variable. Among women who had the OGTT, each 10 unit increase in the fasting glucose value was associated with a 41.1 gram increase in birth weight, p=0.04. Increased fasting cholesterol and glucagon levels were not associated with mean birth weight or LGA but were associated with increased risk for SGA. The occurrence of the latter outcome increased by 16% for each mg/dL unit increase in fasting cholesterol. Fasting insulin, free fatty acid and HDL values were not associated with any birth weight outcome. Only one metabolic variable, fasting free fatty acid level in women with an OGTT, was associated with preterm birth, reducing risk by 95% (CI: 0.01-0.86).

Relationships between maternal glucose level by category and birth outcome variables

There was a significant linear trend between maternal glucose category, and gestational age, mean birth weight and the percentage of LGA, but not SGA (Table 6c.). Among

women without GDM, mean gestational age increased slightly but significantly with increasing glucose category, ranging from 39.2 weeks among women with a glucose level of <100 mg/dL to 39.7 weeks among women with a glucose level of >129 mg/dL; $p=0.01$. Women with GDM had shorter gestations, with a mean of 38.5 weeks. Birth weights that were unadjusted for gestational length followed a similar trend, ranging from 3336.7 grams to 3474.9 grams for women without GDM in the lowest to the highest glucose categories ($p<0.001$), decreasing to 3396.7 grams for infants born to mothers with GDM. After adjustment for gestational age at delivery maintained the linear increase in birth weight among infants of non-GDM mothers, (ranging from 3357.9 grams to 3474.9 grams) but continued that trend among infants of GDM mothers, whose adjusted birth weight rose to 3519.6 grams; $p<0.0001$. The significant linear increase in birth weight with increasing glucose level was maintained after further adjustment for maternal BMI, age, parity, hypertensive disorders, anemia and family history of diabetes; $p<0.0001$.

Among women without GDM, the percentage of LGA increased from 6.2% among women with the lowest glucose levels to 13.1% among those with the highest; $p<0.01$. Women with GDM had somewhat fewer (11.8%) LGA infants than women with abnormal glucose who were not diagnosed with GDM. The pattern for SGA was inversely, but not significantly associated with glucose category. Only 5.2% and 5.3% of women in the lowest and middle categories of glucose had SGA infants, and this percentage declined further to 3.4% of women with glucose values >129 mg/dL and to 1.5% of infants of mothers with GDM; $p<0.15$. Women without GDM were significantly less likely than women with GDM to have preterm births. Among women without GDM there was a significant trend toward decreased preterm birth, ranging from 7.9% of women in the lowest, to 3.4% of women in the highest, glucose category ($p=0.04$). However, 19.1% of infants born to mothers with GDM were preterm.

Other adverse maternal and infant outcomes

Table 6.d examines the means and percents of selected maternal and infant outcomes among non-GDM and GDM mothers by categories of glucose screen data. Among these women without GDM or diabetes, some maternal or infant outcomes appeared to have a higher prevalence or higher mean value as the severity of abnormality in glucose status increased. However, these differences failed to achieve statistical significance in tests for trend. There were differences between results for non-GDM mother and those with GDM.

AIM 4 stated as Hypothesis 1

Among non-diabetic mothers, increased central body fat distribution and an increasingly abnormal maternal metabolic profile (glucose, insulin, free fatty acids, triglycerides) will be associated with increasing birth weight (adjusted for gestational age), infant BMI, birth weight ratio and incidence of large-for-gestational age (LGA) births. The impact of sociodemographic characteristics, prepregnancy BMI, pregnancy

weight gain, other maternal health conditions and prenatal care will attenuate but not account for all of this relationship.

We assessed these relationships with birth weight, LGA, SGA and preterm birth, but not infant BMI or birth weight ratio.

Among non-diabetic mothers, there were significant linear trends toward increasing birth weight and increasing incidence of LGA as maternal glucose level became increasingly abnormal (<100 mg/dL, 100-129 mg/dL and >130 mg/dL, respectively.) When examined categorically, this relationship was attenuated, but did not disappear. When these relationships were examined as continuous variables (glucose value at the 1 hour screen test as a predictor of mean birth weight, adjusted for gestational age), increasing glucose value continued to be significantly associated with increasing birth weight. Other metabolic variables derived from the same blood samples (insulin, insulin-to-glucose ratio, triglyceride, whole and HDL cholesterol) were not significant predictors of birth weight or of LGA. Among women who had an abnormal screening glucose value, increasing fasting glucose value significantly increased mean birth weight and decreased the risk of SGA. The risk of LGA was not significantly influenced by fasting glucose value. Increasing fasting total cholesterol was associated with an increased risk of SGA and increasing free fatty acid was associated with a significantly decreased risk of preterm birth. No other fasting variables were significant.

Aim 4, hypothesis 1 also was designed to assess whether the influences of maternal metabolic and central body fatness variables on birth weight would remain significant predictors of birth weight after adjustment for the effects of variables more typically used in birth weight analyses. Only values that were significantly associated with at least one of the birth weight outcomes were included in the subsequent analyses. This excluded all sociodemographic and health variables available for analysis, except maternal multiparity and age. Prenatal care adequacy was only associated with preterm birth and so was included in the models for that outcome. Several metabolic and anthropometric variables were also excluded, including insulin, insulin-to-glucose ratio, and cholesterol, waist-to-hip ratio mean and values > 0.9. Triglyceride was retained in the models, along with waist and hip circumferences, upper arm circumference, triceps skinfold, upper arm fatness area (UAFA), maternal height, BMI and weight gain.

Multicollinearity among anthropometric variables (in particular BMI and other measures of fatness) made it difficult to determine their independent effects if included in models together. The results of these analyses indicated that measures of central adiposity such as waist and hip circumference were significantly associated with mean birth weight and LGA in multivariate models that did not include BMI but that did include weight gain. Increased upper arm circumference was associated with increased birth weight in models that excluded BMI. BMI, height and weight gain were also significant predictors of all birth weight outcomes when the other anthropometric variables were excluded.

In the final models (Table 7), which included parity, BMI, height, weight gain, hip circumference and glucose value, all variables had significant effects on birth weight,

except hip circumference, which was marginally significant. Glucose had a significant independent effect on mean birth weight, accounting for 15.9 grams of increased birth weight for each 10 mg/dL increase in glucose value ($p=0.01$), after adjusting for the other variables in the model. Glucose value was not significantly associated with LGA or SGA in the final models.

Triglyceride, triceps skinfold and UAFA were not significantly associated with any outcomes. The only significant factor predicting preterm birth was adequate prenatal care, which increased risk by almost 2.5 times.

AIM 5 stated as Hypothesis 2

As maternal central body fat distribution increases and metabolic profile becomes increasingly abnormal, the incidence of adverse maternal and neonatal outcomes will increase, after accounting for prepregnancy BMI, other maternal health conditions and infant gestational age.

No multivariate analyses of adverse other maternal or infant outcomes are reported here. Prevalence rates for these events are reported in Table 4b and relationships with glucose status categories are reported in Table 6d.

AIM 6 stated as Hypothesis 3

Adding central body fat distribution, metabolic characteristics and prenatal treatment variables will result in a better fitting model predicting birth weight and gestational age outcomes than traditional models based on sociodemographic, medical risk and prenatal care use.

This hypothesis was partly proven. Anthropometric variables, including BMI and pregnancy weight gain, along with some measures of central body fat such as waist and hip circumferences, and glucose level were significant predictors of birth weight outcomes (mean birth weight, LGA and SGA). When both BMI and waist or hip variables were in the models, BMI was more consistently associated with birth weight outcomes. Height, which is often excluded from models of birth weight, had a significant independent effect on birth weight but not LGA or SGA. A wide range of sociodemographic variables (including maternal age, educational level, marital status, and several acculturation measures) were not significantly associated with any of the birth weight or gestational age outcomes. Prenatal care adequacy was not associated with mean birth weight, LGA or SGA, but was adequate care was a significant predictor of preterm birth. No other prenatal treatment variables were available for analysis.

Tables