Literature Review

Large-for-gestational age & Related Complications

LGA birth and its associated complications during labor and delivery are the most frequent and serious forms of morbidity for infants to women with GDM. Macrosomic fetuses in diabetic pregnancies acquire central deposition of subcutaneous fat in both the abdominal and interscapular areas. This results in larger shoulder and extremity circumferences, and a decreased head-to-shoulder ratio. Significantly higher body fat and thicker upper-extremity skinfolds are also characteristic of these infants. However, because fetal head size does not increase, shoulder and abdominal girth can become augmented, making vaginal birth risks more common.[7]

If the baby becomes wedged in the birth canal, labor may take more time and instrumental delivery may be necessary. As such, unplanned or emergency cesarean section are sometimes required. Mothers delivering LGA infants are at a greater risk for laceration of the vaginal tissue as well as perineal tears. Larger than normal babies can also lead to uterine atony, where the uterus muscle does not contract appropriately, thereby causing heavy bleeding.[7]

The risks of a LGA birth are not limited to the mother as many fetal risks can present too. One of the most serious problems of vaginal deliveries is shoulder dystocia. It occurs when the fetal shoulders do not deliver after the head has emerged from the vaginal canal. One or both shoulders becomes impacted against the bones of the maternal pelvis. Shoulder dystocia is considered an obstetric emergency, and can lead to fetal death if the infant is not delivered expediently.[17]

In a 2013 study conducted by Ouzounian et al, 221 cases of shoulder dystocia from a cohort of 13,277 vaginal deliveries were assessed and demonstrated that more than half (50.7%) took place in the delivery of LGA infants.[18] Furthermore, when compared side by side, infants of

diabetic mothers (both gestational and pre-gestational) have an increased risk of shoulder dystocia even with normal birthweight. The authors proposed that this could be due to the potential dysmorphic features including thicker upper extremity skinfolds, higher body fat, and broader shoulders often seen in these babies.[18]

Macrosomia is also associated with excessive rates of neonatal morbidity. Macrosomic neonates have higher rates of both hypoglycemia and neonatal jaundice when compared to the infants of mothers without diabetes.[7] A retrospective cohort study of women with type 2 diabetes or GDM and their singleton neonates found that the incidence of neonatal hypoglycemia was 18% and was statistically associated with birth weight and macrosomia.[19] Neonate hypoglycemia occurs as a result of the hyperinsulinemia in utero as a response to the high blood glucose levels from the mother. While less common, it can lead to serious complications including central nervous system and cardiopulmonary disorders.

Gestational Diabetes Mellitus

A recent study by Desisto et al. indicated that GDM prevalence is as high as 9.2% in the United States, the highest prevalence observed in the world.[20] Furthermore, these rates have increased with the steady rise of obesity and type 2 diabetes.[20,21] A recent study collecting hospital discharge data from 1994 to 2004 found that rates of GDM increased by 56% in the ten-year time frame.[22] In the United States, rates of GDM are highest in Asian, non-Hispanic black, Native American, and Hispanic women and lowest in Non-Hispanic white women.[23]

Risk factors associated with GDM include pre-pregnancy overweight or obesity, advanced maternal age, being from various minority race/ethnicity groups, multipara, and GDM in the previous pregnancy.[24,25] Interestingly, a history of GDM is one of the most reliable risk factors concerning the development of type 2 diabetes for the mother later on.[26]

Gestational diabetes mellitus is defined as glucose intolerance with an onset or diagnosis taking place during pregnancy.[27] In a recent study evaluating 7,415 diabetic and non-diabetic mothers, the rate of LGA among DM and non-DM was 23.7% and 10.5%, respectively.[28] The exact mechanisms behind GDM are unclear, however, the maternal and fetal-placental factors' interaction have been studied at length.[27, 29]

The placenta size increases as gestational age advances and with it, there is a rise in level of estrogen, progesterone, cortisol, and placental lactogen in the maternal blood supply. Beginning at 20 to 24 weeks of gestation, this is accompanied by an increase in insulin resistance that approximate the insulin resistance observed in people with type 2 diabetics. When the mother delivers the fetus, the placental hormone production stops and the insulin resistance abates.[30] This observation strongly suggests that these hormones dictate the difference in insulin resistance compared to what takes place in a healthy pregnancy.

Human placental lactogen increases 10-fold during the second half of pregnancy and stimulates lipolysis. This causes the mother to use free fatty acids as an alternative fuel source, thereby conserving glucose and amino acids for the fetus. In turn, the mobilization of free fatty acids interferes with the insulin-directed entry of glucose into cells. For this reason, human placental lactogen is considered an antagonist of insulin action during pregnancy.[7]

Pedersen's hypothesis is used to explain the pathophysiology of LGA infants. This hypothesis is based on the fact that glucose, when elevated, crosses the placenta. The maternal-derived insulin, however cannot. Consequently, in the second trimester, the fetal pancreas which has developed to secrete insulin, responds to high blood glucose. Even more, it does so in an automated manner, regardless of glucose stimulation leading to hyperinsulinemia. This

combination of hyperinsulinemia and hyperglycemia causes glucose to be stored as adipose and protein tissue.[7]

Adipose tissue also plays a role in the development of GDM. This tissue produces adipocytokines, including leptin, adiponectin, tumor necrosis factor, and interleukin-6, as well as resistin, visfatin, and apelin.[31,32] Adipocytokines and elevated lipid concentrations have been associated with insulin resistance in both pregnant and non-pregnant women. Evidence suggests that one or more of these components may impair insulin signaling.[33]

Data from the 1991 Diabetes in Early Pregnancy Study discovered that fetal birth weight is most closely correlated with second and third-trimester postprandial blood sugar levels. This study found that when postprandial glucose values average 120 mg/dl or less, approximately 20% of infants can be expected to be born LGA. Furthermore, if the glucose values are as high as 160 mg/dl, the rate can reach up to 35%.[34] In another study evaluating the Mediterranean population, the adjusted odds ratio associated with one standard deviation increase (7 mg/dL) in the fasting plasma glucose was 1.26 for LGA infants.[35] If a woman had a fasting glucose of 157 mg/dL, her odds of having an LGA infant would be 1.26 times greater than that of a woman with a fasting glucose of 150 mg/dL. Even more, a prospective mother-offspring multiethnic cohort study of 1247 mothers (57.2% Chinese, 25.5% Malay, 17.3% Indian) discovered that with each standard deviation increase in fasting glucose, there was a 1.64 increased odds ratio for LGA.[36]

Diagnosis of GDM

Diagnosis of GDM was first proposed in 1964 to be an assay of whole blood glucose during a 3-hour oral glucose tolerance test (OGTT). Glucose levels of 90, 165, 145, and 125 mg/dl for fasting, one-hour, two-hour and three-hour post glucose load respectively, were proposed for the diagnostic thresholds. Adjustments have been made over the years based on

data from women who were diagnosed with diabetes after gestation.[37] Spectrum Health system uses the American Diabetes Association (ADA) recommended diagnostic criteria. In this criteria, diagnosis is made if two or more of the venous plasma concentrations are met or exceeded. These are 95, 180, 155, 140 mg/dL for fasting, one hour, two hour, and three hour fasting, respectively.[38]

In its' most recent position statement, the ADA suggested that all pregnant women be screened for GDM between the 24th and 28th week of gestation, unless they are low risk. Low risk women include those that are younger than 25, normal pre-gestational weight, member of an ethnic group with low prevalence of diabetes, have no history of glucose intolerance and poor obstetrical outcomes, and no known diabetes in first degree relatives.[37]

Pre-Pregnancy BMI and Risk of LGA infants

One in three adults in the U.S. are obese so it is not surprising that obesity is becoming the most common complication of pregnancy and the predominant risk factor for maternal mortality in developed countries. Women who are obese prior to pregnancy may suffer poor health before, during, and after pregnancy which may affect their birth outcomes as well as their willingness or ability to breastfeed.[39]

One explanation for the link between birth weight outcomes and maternal weight is the fetal origins hypothesis, similar to the Pedersen hypothesis formulated in 1954. The fetal origins hypothesis posits that pre-pregnancy obesity causes greater concentrations of glucose and fatty acids to be delivered to the developing fetus. The resulting increase in fetal insulin accelerates fetal growth and leads to high birth weight. Consistent with this hypothesis, it has been shown that women who are overweight or obese at the start of their pregnancy are at increased risks for LGA infant and macrosomia.[39]

In one Chinese study, the odds of delivery of LGA for overweight or obese pregnant women were 2 and 3.8 times greater than normal weight women, respectively.[40] In another study, researchers analyzed data for 276, 436 deliveries in 23 developing countries throughout the world. Higher maternal age (20-34 years), body-mass index, and presence of diabetes were associated with significantly increased risk of macrosomia. In all regions, maternal BMI of 35 kg/m^2 or greater had substantially higher odds for delivering a macrosomic infant than did those with a BMI less than 30 kg/m^2.[41] The results of these studies suggest that primary prevention of overweight/obesity in women of childbearing age may be an important strategy to reduce the number of LGA newborns, and consequently, the long-term public health burden of obesity.

Role of Sociodemographic & Socioeconomic Factors on Prenatal Risk

There is a large body of evidence illustrating the link between socioeconomic status and birth risk. Socioeconomic disparities in birth outcomes are pervasive and take place at both the individual and community level. A prospective cohort study in Canada used information from maternal questionnaires and medical records and found significant associations between lower socioeconomic status and increased risk of macrosomia with higher pre-pregnancy BMI at both the individual and neighborhood level. The neighborhoods were distinguished by census data and closely resemble U.S. zip codes.[42] Another study using data for 28,722 live births in Shaanxi, China from 2010-2013 discovered that rates of LGA were higher in those of low socioeconomic status.[43]

While countless studies have examined the association between low socioeconomic status and low birth weight, preterm deliveries, and infant death is extensive, there lacks an analysis of low-socioeconomic status and risk of delivering an LGA infant.

Race/Ethnicity & Poor Outcomes

To explain the disparities that exist in birth outcomes using the weathering hypothesis proposal of cumulative experiences of social inequality and racism, studies have suggested that chronic stress associated with everyday interpersonal and institutional racism may have an impact on birth outcomes of minorities. Recent data has showed that non-Hispanic Black and Hispanic women experience the highest likelihood of having a low birth weight (LBW) or preterm infant. These groups of women also have the highest rates of infant and maternal mortality.[16]

Unfortunately, few studies have evaluated if risk of LGA infants to women with GDM varies by race/ethnicity or by income level. Studying such disparities is important from a public health standpoint to develop individualized approaches for managing GDM. In doing so, risks to mothers and their infants could both be improved.

As previously mentioned, incidence of GDM is highest in Asian and non-black Hispanic women and lowest in African American and white women.[23] These disparities are surprising given that obesity, the strongest known risk factor for GDM, is highest in African Americans and lowest in Asians.[44]

There remains conflicting research on the racial and ethnic disparities in risk for macrosomia to women with GDM. A retrospective cohort study found that among Hawaiian women with GDM, the highest prevalence of macrosomia was in white women (14.5%), while the lowest was in Filipina women (5.3%).[45] Another study evaluating a wider range of racial/ethnic groups found that the highest risk of LGA were infants born to non-Hispanic black women (17.2%), followed by those to Pacific Islander (16.2%), Hispanic (14.5%), non-Hispanic

white (13.1%), Asian Indian (12.8%), Filipino (11.6%), and other Asian (9.6-11.1%) women.[46] These findings were consistent with another California study that demonstrated highest rates of LGA newborns to African American women (25.1%), lowest rates in Asian women (13.9%), and intermediate among Hispanic (17.9%), white (16.4%), and Filipina women (15.3%).[47] In most racial and ethnic groups, the highest increased risk of LGA newborns was to women with class II obesity. Furthermore, African American and Asian women in that BMI category had a four-fold increased risk of LGA newborns compared to women in the same racial and ethnic group but of normal weight.[47]

Contrary to these findings, a 2017 retrospective cohort analysis of births in Texas between 2006 and 2011 found that the risk of GDM increased as BMI increased for all racial/ethnic groups but that the rate of LGA was lowest in the non-Hispanic Blacks and Asians compared to Whites and Hispanics.[48]

These studies suggest that the perinatal outcomes in women with GDM differ by race/ethnic group. Together, they demonstrate the need for additional research so further evidence can support the identification of different counseling techniques for women. Because being overweight and obese are risk factors for both developing gestational diabetes mellitus as well as independently for having an infant born LGA, it is likely the rates of both will increase. Even more, the increased rate of GDM and LGA will likely draw the attention of health care practitioners, thereby requiring uniform diagnostic measures. In addressing the role of race/ethnicity and socioeconomic status on the risk of LGA infants born to women diagnosed with GDM, this study could better direct public health interventions. Because the health of mothers and their infants is indicative of the future health of communities, it is crucial that the health care system understand the disparities at play.