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Maternal metabolic adaptations to pregnancy among young women in Cebu, Philippines

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Abstract

Objectives: Evidence that fetal development has long-term impacts on health has increased interest in maternal-fetal nutrient exchange. Although maternal metabolism is known to change during gestation to accommodate fetal nutrient demands, little is known about these modifications outside of a Western, clinical context. This study characterizes maternal metabolic adaptations to pregnancy, and their associations with offspring birth weight (BW), among women living in the Philippines.

Methods: Fasting glucose, triglycerides, insulin, leptin, and adiponectin were assessed in 808 participants in the Cebu Longitudinal Health and Nutrition Survey (Metropolitan Cebu, Philippines). Cross-sectional relationships between metabolites and hormones and gestational and lactational status were evaluated. Among the subset of currently pregnant women, associations between maternal glucose and triglycerides and offspring BW were also examined.

Results: Women in their second and third trimesters had significantly lower fasting glucose and adiponectin compared to nulliparous women, and leptin levels and triglyceride levels were notably higher late in pregnancy (all $P < .05$). Among pregnant women, fasting glucose was a positive predictor of offspring BW, but only in males ($P = .012$, $R^2 = .28$). Hormones and metabolites in post-partum women trend back toward levels found in nulliparous women, with some differences by breastfeeding status.

Conclusions: We find evidence for marked changes in maternal lipid and carbohydrate metabolism during pregnancy, consistent with known adaptations to support fetal growth. The finding of sex-specific relationships between maternal glucose and offspring BW adds to evidence for greater impacts of the maternal-gestational environment on biology and health in male offspring.

1 | INTRODUCTION

Evidence that fetal nutrition and growth have long-term impacts on future biology and disease risk (Barker, 1994; Barker, Osmond, Golding, Kuh, & Wadsworth, 1989; Cameron & Demerath, 2002) has increased interest in the maternal factors that shape the intrauterine nutritional milieu. Although the mother's dietary intake of both micro- and macronutrients contribute to fetal growth, especially in populations experiencing severe nutritional stress (Ceesay et al., 1997; Prentice, Cole, Ford, Lamb, & Whitehead,

1987, 2000), past attempts to increase birth weight by supplementing the macronutrient intake of pregnant women have had little success (Kramer & Kakuma, 2010). For instance, a meta-analysis of published intervention trials found that even large increases in protein and calorie intake typically yield a roughly 1 ounce average increase in offspring birth weight (Kramer & Kakuma, 2010). The modest changes in fetal growth resulting from sizeable increases in maternal dietary intake point to factors other than diet during pregnancy as important for shaping maternal-fetal nutrient exchange.

Glucose is the primary energy substrate for the growing fetus, and hormone-driven shifts in maternal metabolism during pregnancy help meet the glucose demands of the growing fetus (Angueira et al., 2015; Catalano & De Mouzon, 2011). Fasting glucose during pregnancy is a consistent and strong predictor of offspring birth weight, demonstrating the close relationship between circulating concentrations of this nutrient and fetal growth (HAPO Study Cooperative Research Group, 2008; Sasson, Vitins, Mainigi, Moley, & Simmons, 2015). Maternal triglycerides also contribute to fetal growth, albeit indirectly, by providing an alternative maternal energy source to promote preferential glucose uptake by the fetus (Catalano & De Mouzon, 2011; Herrera & Lasuncion, 2012).

Changes in maternal metabolism during pregnancy coordinate changes in the storage and mobilization of energy substrates. Maternal glucose and insulin production increase in early pregnancy to facilitate energy storage in adipose tissue, which prepares the mother's body for higher energy demands in later gestation and lactation (Stuebe, 2015). Although glucose production increases at this time, fasting levels of both glucose and insulin are lower than in the pre-pregnancy state due to more rapid maternal glucose uptake into peripheral tissues and the diluting effects of steadily increasing plasma volume (Catalano & De Mouzon, 2011; Ogato, 2012).

The second half of gestation is marked by the initiation of a catabolic, energy-releasing state that facilitates increased glucose transfer to the growing fetus. This occurs through two main pathways. First, mobilization of previously accumulated energy stores is promoted by rising levels of the hormone leptin, which sends a signal to the mother's brain that facilitates fat catabolism by effectively mimicking weight gain (Herrera & Lasuncion, 2012). Increased production of estrogen and human placental lactogen (hPL) suppress adiponectin, further promoting maternal peripheral insulin resistance while increasing levels of triglycerides through the breakdown of maternal fat stores (Fuglsang, Skjaerbaek, Frystyk, Flyvbjerg, & Ovesen, 2006). Maternal fasting triglycerides increase steadily across pregnancy, and have been found to reach levels higher than 250% of pre-pregnancy levels by the end of gestation (Chehab, 2014). This dramatic rise in triglycerides allows for a major shift in maternal metabolic substrate use from glucose to triglycerides, serving as an important pathway for shunting greater quantities of glucose to the growing fetus (Catalano and DeMouzon, 2011; Kitajima et al., 2001; Vrijkotte, Algera, Brouwer, van Eijsden, and Twickler, 2011).

The extent of glucose transfer is dependent upon the maternal-fetoplacental concentration gradient, meaning that more glucose will be drawn from maternal circulation when either fetal glucose levels decline or maternal levels increase (Angueira et al., 2015). This passive transport of glucose is facilitated by several glucose transporters (Illsley, 2000; Jansson, Wennergren, & Powell, 1999). Glucose transporter-1 (GLUT-1), the major glucose transporter, exhibits a 10-fold increase in expression on the maternal-facing side of the placenta and a 50% increase in activity during the second half of pregnancy (Jansson et al., 1999; Poston, 2011). Other glucose membrane transport proteins, including GLUT-2, -3, -4, and -12, are also active in the placenta during gestation (Jansson & Powell, 2000). As glucose crosses the placenta, it stimulates fetal production of insulin and IGF-1 (insulin-like growth factor 1), which fuels lean body growth (second and third trimester) and fat deposition (3rd trimester) (Angueira et al., 2015; Haig, 1993; Pedersen, 1952; Pinney & Simmons, 2012). The effect of maternal glucose levels on offspring birth weight is dose-dependent, from levels within the normal clinical range to the abnormally levels that characterize gestational diabetes mellitus (Galliano & Bellver, 2013; Kitajima et al., 2001; Sasson et al., 2015).

The close association between maternal glucose and birth weight, in conjunction with the minimal impact of maternal diet supplementation, suggests that maternal metabolism has the capacity to significantly buffer fetal nutrient supply (Kuzawa & Thayer, 2012). Such a safeguard helps ensure adequate nutrient flow under nutritionally challenging conditions (Rutherford, 2012; Wells, 2007), but also minimizes the positive response to any temporary increase in intake (Kuzawa, 2005). Because fetal nutrition and growth predict future disease risk, it can be posited that the factors that regulate maternal metabolism during gestation may be more important, compared to maternal pregnancy diet itself, as predictors of future health (Benyshek, 2013; Kuzawa & Thayer, 2012; Wells, Chomtho, & Fewtrell, 2007.

After parturition, lactation imposes a significant metabolic burden marked by a 15%-25% increase in energy expenditure, and is characterized by a shift in maternal metabolism that mobilizes fat stores accumulated during pregnancy to sustain these extra costs (see Stuebe, 2015, for review). Most pregnancy-supporting hormones return to pre-pregnancy levels within a few weeks after birth, regardless of breastfeeding status. However leptin, an indicator of energy stores, is directly related to maternal body weight, both of which have been observed to decrease more rapidly among women who are breastfeeding (Butte, Hopkinson, Mehta, Moon, & Smith, 1999). As leptin slowly returns to baseline, adiponectin levels are suppressed to below pre-pregnancy levels among lactating women by the action of prolactin, the primary hormone involved in both mammary development and lactation maintenance (Gunderson et al., 2014; Stuebe et al., 2011). Maternal triglyceride levels likewise return to pre-pregnancy levels earlier among lactating women, as has

also been shown for glucose tolerance and insulin sensitivity (Darmady & Postle, 1982; Stuebe, 2015).

The majority of past studies of maternal metabolic adaptations to pregnancy have focused on the increasingly common occurrence of diabetes among overweight or obese women, which can have the effect of "overfeeding" the baby and increasing intergenerational risk for excess weight gain in offspring (HAPO Study Cooperative Research Group, 2008; Schwartz et al., 1994). Here, we report levels of glucose, triglycerides and metabolic hormones in a large but relatively lean sample of young adult women living in the Philippines. In this study, we document metabolic differences by reproductive status, including by trimester of gestation and during lactation. Among the subset of women who were pregnant during the survey, we also evaluate maternal fasting glucose and triglyceride levels as predictors of offspring birth outcomes.

2 | METHODS

2.1 | Study population

Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a longitudinal birth cohort of participants born between 1983 and 1984 in Metropolitan Cebu, Philippines (Adair et al., 2011). The current study used metabolic, reproductive, anthropometric, and socioeconomic data from 808 women (avg. age = 21.5 years) collected in 2005. Reproductive histories on the same women were subsequently collected in 2007 and were used (1) to identify women who reported to not be pregnant in 2005 but were either not yet aware or did not accurately report their pregnancy status and (2) to, when available, obtain birth weights of offspring of women who were pregnant during the 2005 survey (for more see Thayer, Feranil, & Kuzawa, 2012). A total of 17 offspring birth weights were not available because some women were not recontacted during the 2007 survey or their pregnancies did not terminate in a singleton liveborn who had their birth weight measured at delivery. In addition, one female newborn was a high-leverage outlier in models linking maternal glucose to offspring birth weight, and was therefore removed from the analysis sample. Gestational ages of offspring were estimated based on the mothers' date of her last menstrual period. Participants with type II diabetes mellitus (diagnosed by oral glucose tolerance test), those who did not fast for at least 12 hours prior to the time of blood draw, or those who delivered preterm, twins, or other multiple births were excluded from analyses.

This research was conducted under conditions of written informed consent with approval of the Institutional Review Boards of the University of North Carolina at Chapel Hill (Chapel Hill, North Carolina), Northwestern University (Evanston, Illinois), and the Office of Population Studies Foundation (Cebu, Philippines).

2.2 | Metabolic measurements

Blood samples from venipuncture were collected using EDTA-coated vacutainer tubes in the homes of participants in the morning after an overnight fast (~12 hours). Samples were then centrifuged to separate plasma prior to freezing at $-35°C$ after being kept on ice packs in coolers for no more than 2 hours. Samples were shipped on dry ice to several laboratories in the United States, where they were stored at $-80C$ until analysis.

Fasting blood glucose was measured at the time of venipuncture with one drop of blood on site using a portable glucose meter (One Touch Ultra Blood Glucose Monitoring System, Johnson and Johnson) (for details see Norris et al., 2012). Triglycerides were measured using enzymatic methods with reagents from Beckman Diagnostics on the Beckman Diagnostics CX5 chemistry analyzer (Palo Alto, CA) at the Emory Lipid Research Laboratory (for more see Feranil, Duazo, Kuzawa, & Adair, 2011). The Emory Lipid Research Laboratory is a participant in the CDC/NHLBI Lipid Standardization Program to ensure accuracy and precision of the measurements. Serum adiponectin levels were measured using a modified DuoSet ELISA kit (Catalog Number DY1065) (see Wu et al., 2010), and fasting plasma leptin levels were analyzed with the Linco Human Leptin Elisa kit (Catalog Number EXHL-80SK) in duplicate at the Laboratory for Human Biology Research, Northwestern University. Finally, fasting insulin levels were measured using automated Siemens Centaur XP clinical chemistry analyzer methods (Pearson et al., 2003) at the Department of Pathology and Laboratory for Medicine at Evanston Northwestern Healthcare.

2.3 | Anthropometric measurements

Maternal height, weight and skinfold thicknesses (triceps and subscapular) were measured using standard anthropometric techniques (Lohman, Roache, & Martorell, 1992). We calculated maternal body mass index (BMI) as the ratio of weight (kg) to height (m^2).

Offspring birth weights were obtained from the mothers as part of routinely-updated reproductive histories. For this study, we only used birth weights from births in which the newborn was weighed at birth. Most women had birth records that they could refer to when answering this question, although we did not have information to know which women provided records or simply recalled their baby's weight. To test reliability of recalled data, we utilized data

TABLE 1 Characteristics of CLHNS female participants[a]

	All (n = 808)	Nulliparous (n = 472)	Pregnant (n = 97)	Post-Partum (n = 239)	P-value[b]
Age (years)	21.5 (0.3)	21.5 (0.3)	21.4 (0.3)	21.5 (0.3)	.49
Height (cm)	151.2 (5.5)	151.5 (5.6)	151.0 (5.2)	150.7 (5.3)	.11
Weight (kg)	46.6 (8.1)	45.7 (8.2)	47.0 (7.5)	48.4 (8.0)	.0001**
BMI (kg/m²)	20.4 (3.2)	19.9 (3.2)	20.6 (3.0)	21.3 (3.1)	.0001**
Sum of Skinfolds (mm)[c]	39.4 (12.2)	39.4 (12.4)	38.3 (10.9)	39.7 (12.6)	.62
Arm Circumference (cm)	25.3 (3.0)	25.1 (3.1)	25.0 (2.7)	25.8 (3.0)	.007**
Waist-to-hip ratio	0.89 (0.05)	0.88 (0.04)	0.93 (0.06)	0.90 (0.5)	.0001**
Household income (pesos/wk)	637 (1614)	767 (2058)	427 (418)	467 (550)	.03*
Household assets (score, 1–11)	5.2 (2.0)	5.7 (1.8)	4.3 (1.8)	4.5 (2.0)	.0001**
Educational attainment (years)	11.4 (3.3)	12.4 (3.1)	9.9 (3.1)	9.9 (2.8)	.0001**
Urbanicity (score, 1–70)	41.3 (13.1)	42.1 (12.7)	41.1 (13.5)	39.6 (13.5)	.04*

[a]All mean (SD); *P < .05, **P < .01.
[b]Significance of differences across reproductive status groups from one-way ANOVA.
[c]Sum of triceps and subscapular skinfolds.

available in a subsequent study in this sample that included matched maternal recalled birth weights and interviewer-assessed weights measured several days after birth (data not shown). Adjusting for the day after birth of the interviewer's measurement, the partial correlation between the two measures was 0.83, suggesting relatively high reliability of the recalled measures consistent with the findings of a recent meta-analysis of recalled birth weight (Shenkin et al., 2016).

2.4 | Statistical analysis

Stata 13.1 (College Station, TX) was used to conduct all analyses. We performed one-way ANOVA analyses to test differences in maternal age, height, weight, BMI, skinfolds, income, assets, education, and urbanicity scores by current reproductive status (nulliparous, pregnant, and post-partum). We conducted multiple regression analyses to test for differences in maternal metabolic biomarkers across reproductive status and trimesters. We considered P-values of <.05 as statistically significant, but also discuss borderline relationships (P < .1). The effects of maternal fasting glucose and triglycerides on offspring birth weight stratified by sex were also evaluated using multiple regression analyses, controlling for parity, gestational month at time of blood draw, and maternal smoking status. For this study, maternal smoking status was coded as a binary, "yes" or "no" smoking during pregnancy.

3 | RESULTS

At the time of data and sample collection, more than half of the eligible participants were nulliparous (n = 472), 239 were three years post-partum or less, and 97 were currently pregnant (n for trimesters 1–3 = 38, 39, and 20, respectively). Pregnant women included in analyses of effects of fasting glucose on offspring birth weight (n = 80) did not differ significantly from other pregnant women included in the study, or from women of other reproductive statuses, with respect to age, height or skinfolds. However, pregnant women were heavier, and had lower educational attainment, household income, and assets than nulliparous women (Table 1).

Figure 1 plots average maternal metabolic measures against reproductive status for nulliparous, currently pregnant, and parous but not currently pregnant women through post-partum (PP) year 2. Overall, our analyses demonstrate maternal metabolic adaptations to pregnancy and lactation through differences in energy substrate and hormone levels across reproductive status (Table 2 and Figure 1). Compared to nulliparous women, glucose levels in the first trimester were moderately lower, with levels becoming significantly lower in the second and third trimesters. Triglycerides, on the other hand, showed a significant increase in the second trimester, with the magnitude of augmentation peaking during the third trimester. Leptin was higher among women in
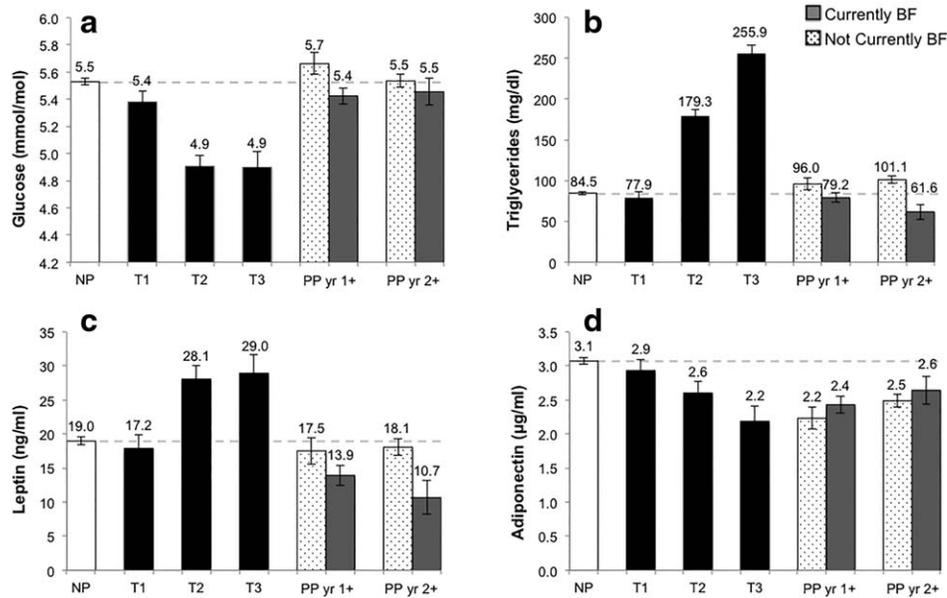
FIGURE 1 Mean fasting energy substrate (a and b), and hormone levels (c and d) among women varying in current reproductive status, $n = 808$. Error bars = standard deviation; NP = nulliparous; PP yr = post-partum year; T1-T3 = trimester 1–3; BF = breastfeeding

their second and third trimesters, coupled with significantly lower levels of adiponectin during this period of gestation as compared to nulliparous women. Insulin was only borderline significantly lower during the second trimester.

Findings among women in the post-partum period differ between women who were breastfeeding and those who were not, consistent with metabolic adaptation to lactation (Table 2). Compared to nulliparous women, triglyceride levels were significantly lower among women who were breastfeeding during post-partum year 2, and higher among those who were not (Table 2). Adiponectin was found to be lower during post-partum years 1 and 2, regardless of breastfeeding status, while leptin levels were only lower among those who were breastfeeding.

Fasting glucose significantly predicted male offspring birth weight, explaining approximately 28% of the variance in birth weight (Table 3 and Figure 2), controlling for maternal parity, age, gestational age at blood draw, and smoking status. There was a significant interaction between offspring sex and maternal glucose as a predictor of birth weight ($P < .037$, model not shown), with the relationship only significant in male offspring.

4 | DISCUSSION

This study is one of the first to report maternal metabolic adaptations to normal pregnancy and breastfeeding in a non-

TABLE 2 Multiple regression models relating metabolites to current reproductive status ($n = 808$)[a]

	NP	First Trimester	Second Trimester	Third Trimester	PP yr 1, NBF[b]	PP yr 1, BF[b]	PP yr 2, NBF[b]	PP yr 2, BF[b]	R^2
Glucose (mg/dl)	-	−3.0 (1.5)*	−11.2 (1.5)**	−11.3 (2.1)**	2.4 (1.5)	−1.9 (1.2)	0.1 (1.0)	−1.3 (1.9)	0.10
Triglycerides (mg/dl)	-	−6.7 (7.7)	94.8 (7.7)**	171.4 (10.5)**	11.4 (7.6)	−5.4 (5.9)	16.6 (5.0)**	−23.0 (9.4)*	0.35
Insulin (μl/ml)	-	−1.8 (1.3)	−2.5 (1.3)~	−2.4 (1.8)	0.6 (1.3)	−0.6 (1.0)	0.4 (0.8)	−2.2 (1.6)	0.01
Leptin (ng/ml)	-	−1.8 (2.1)	9.1 (2.0)**	10.0 (2.8)**	−1.5 (2.0)	−5.1 (1.6)**	−0.9 (1.3)	−8.3 (2.5)**	0.07
Adiponectin (μg/ml)	-	−0.1 (0.2)	−0.5 (0.2)**	−0.9 (0.2)**	−0.8 (0.2)**	−0.6 (0.1)**	−0.6 (0.1)**	−0.4 (0.2)*	0.08

[a]Multiple regression models adjusted for age at measurement (coeff. not shown); ~$P < .1$, *$P < .05$, **$P < .01$; values= β(SE).
[b]NP = nulliparous, pp = post-partum, BF = currently breastfeeding, NBF = not breastfeeding.

TABLE 3 Multiple regression models relating offspring birth weight to maternal fasting glucose and lipids during pregnancy[a]

	Model 1		P	R^2	Model 2		P	R^2	Model 3		P	R^2
Males (n = 48)												
Glucose (mg/dl)	24.3	(5.6, 43.0)	.01*	0.27					25.1	(6.1, 44.0)	.01*	0.28
Triglycerides (mg/dl)					0.6	(–2.4, 3.7)	.68	0.16	1.1	(–1.8, 4.0)	.46	
Females (n = 32)												
Glucose (mg/dl)	5.2	(–10.5, 20.9)	.51	0.30					5.7	(–10.2, 21.6)	.47	0.32
Triglycerides (mg/dl)					–0.9	(–3.3, 1.5)	.45	0.30	–0.9	(–3.4, 1.4)	.42	

[a]values are β (95% CI). Parity, gestational age, and smoking status were controlled for in all models, *p < 0.05.

clinical, non-Western population. Overall, the Filipino participants in this study displayed expected differences in metabolic measures by gestational and lactational status, pointing to broad adjustments of maternal metabolism in support of fetal growth. We also found evidence for a role of maternal glucose levels as a predictor of fetal growth and birth weight, although these relationships were limited to males.

Late in gestation glucose requirements of the fetoplacental unit rise markedly as fetal growth and fat deposition increase. The rising demand is met, in part, by a shift in maternal metabolism facilitated by increasing insulin resistance promoted by production of placental lactogen (Angueira et al., 2015; Hadden & McLaughlin, 2009). The relatively low glucose levels found among women in the second and third trimester are consistent with previous studies and are likely indicative of the higher rate of fetoplacental uptake in late gestation (Di Cianni, Miccoli, Volpe, Lencioni, & Del Prato, 2003; Felig & Lynch, 1970; Hadden and McLaughlin, 2009).

Increases in maternal glucose production and maternal-fetal transfer are orchestrated in part by changes in the levels and action of adiponectin and insulin. The lower adiponectin levels during the second and third trimesters were consistent with most existing studies (see D'Ippolito, Tersigni, Scambia, and Simone, 2012 for review; Elshoreva, 2011; Paradisi et al., 2010). In the non-pregnant state, adiponectin increases insulin sensitivity, and therefore glucose uptake, in peripheral tissues. However, during late pregnancy adiponectin levels decrease, helping shunt glucose toward the growing fetoplacental unit. In contradiction to our non-significant findings for fasting insulin, prior studies have found that insulin levels often increase in parallel to rising insulin resistance in later pregnancy (Catalano, Roman-Drago, Amini, & Sims, 1998; Sonagra et al., 2014). We can only speculate on possible explanations for this discrepancy between our study and prior findings in other populations. In this regard, it is notable that a global reduction in insulin production is another means (in addition to reducing peripheral insulin sensitivity) of reducing peripheral glucose uptake (Kuzawa, 2010; Peters et al., 2004). One possibility is that the relatively lean state of the women in our sample, as illustrated by their low pregnancy BMIs (mean 20.6), necessitated more
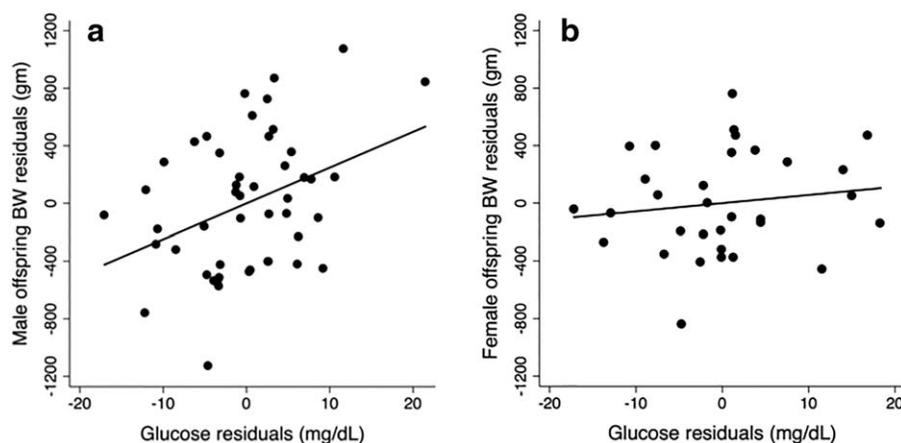

FIGURE 2 Multiple regression models relating maternal fasting glucose and offspring birth weight, plotted separately for male (a) and female (b) offspring. Models control for maternal triglycerides, parity, gestational age, age, and smoking status. Males (n = 48): β = 25.1, P = .01; females (n = 32): β = 5.7, P = .47

aggressive measures to redistribute glucose during pregnancy. Additional work on metabolic adaptations in conditions of marginal nutrition and nutritional status would help clarify this possibility.

At Cebu, fasting triglyceride levels are twofold to threefold higher among women in their second and three trimester compared to nulliparous women. This finding is similar to patterns commonly observed in other populations, and is understood as reflecting maternal mobilization of stored fats late in pregnancy to support rising metabolic needs (for review see Herrera, 2002). The triglyceride surge in late pregnancy is driven in part by increasing placental leptin production, which enters the mother's circulation and induces mobilization of maternal adipose stores. Thus, the elevated leptin levels that we observe among women in the second and third trimesters of pregnancy were expected and are consistent with the role of leptin as a mediator of changes in maternal lipid metabolism (Forhead & Fowden, 2009; Fuglsang et al., 2006; Masuzaki et al., 1997).

Findings among post-partum women were also largely in agreement with previous studies (Darmady & Postle, 1982; Gunderson et al., 2014; Stuebe, 2015). At Cebu we found that both fasting glucose and insulin levels post-partum were not significantly different than those of nulliparous women. These results suggest that glucose metabolism largely returns to a pre-pregnancy state after parturition regardless of breast-feeding status (Gunderson et al., 2014; Stuebe et al., 2011).

Conversely, maternal lipid metabolism has been shown to be more sensitive to breastfeeding status. Women in our study who were breastfeeding had lower triglycerides, and those who were not breastfeeding had higher triglycerides, compared to nulliparous women. Consistent with previous studies these results suggest that lactation is associated with more favorable metabolic parameters post-partum, due in part to the shunting of lipids toward breastmilk production which lowers maternal circulating levels (Chouinard-Castonguay, Weisnagel, Tchernof, & Robitaille, 2013; Gunderson et al., 2012).

Prolactin, the primary hormone related to milk production, also plays an essential role in metabolism by suppressing leptin and adiponectin levels (Asai-Soto et al., 2006). Lower leptin concentrations may increase gluconeogenesis and therefore increase the supply of glucose needed to support lactation (Gunderson et al., 2012). Indeed, we find that leptin levels are significantly lower, compared to nulliparous women, among women who are breastfeeding, but no different from nulliparous women among those who are not breastfeeding. These findings are broadly consistent with previous studies that show an inverse relationship between breastfeeding intensity and maternal leptin levels (Gunderson et al., 2014). Finally, although prolactin is also thought to suppress adiponectin production and secretion from adipocytes, we find that adiponectin is lower among all women post-partum, regardless of breastfeeding status. These adiponectin measures may indicate weight retention despite breastfeeding, although the current literature is inconclusive regarding expected outcomes (Gunderson et al., 2014; Stuebe et al., 2011).

In agreement with previous research, we find that the mother's fasting glucose during pregnancy is a significant and positive predictor of male offspring BW, explaining 28% of BW variance. This positive association between maternal glucose and offspring BW was also observed among female offspring but was not statistically significant. Consistent with prior findings from Cebu, the sex-specific relationship between maternal metabolism and offspring BW points to greater male sensitivity to the intrauterine environment (Kuzawa & Adair, 2004; Lee, Fried, Thayer, & Kuzawa, 2014; Thayer et al., 2012). It has been hypothesized that sex differences in sensitivity to prenatal nutrition may be due to the more rapid and costly growth of male, compared to female, fetuses (Kuzawa & Adair, 2004; Wilkin & Murphy, 2006). However, greater male responsiveness to prenatal nutrition is not universally found (Voldner, Froslie, Godang, Bollerslev, & Henriksen, 2009), and additional work is needed to clarify the general pattern of sex differences in sensitivity to maternal nutrient concentrations and the factors, whether metabolic, epigenetic or otherwise, that explain this variation across studies. In contrast to findings with maternal glucose, relationships between maternal fasting triglycerides and offspring BW were not significant for either sex, which is consistent with the role of the gestational rise in triglycerides as a substitute energy source for the mother's body (Angueira et al., 2015; Chehab, 2014).

The primary limitation of this study is that we infer changes in maternal pregnancy and post-pregnancy metabolism from cross-sectional data obtained from women varying in reproductive status. In addition, our analyses relating maternal metabolites to offspring birth weight were restricted to the subset of women for whom we retrospectively obtained birth outcomes during subsequent surveys. Although this limited statistical power, we identified a strong relationship between maternal fasting glucose and male offspring BW.

In sum, our findings among this young, lean cohort of women living in Cebu Philippines are consistent with an important role of maternal metabolic regulation as an influence on fetal nutrition. Future work should aim to reconstruct historical and developmental factors that drive individual variation in the metabolic adaptations during pregnancy and their short- and long-term impacts on offspring health.

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AUTHOR CONTRIBUTIONS

RLF conducted the statistical analyses and drafted the manuscript. CWK conceived of analysis, advised on statistical analysis, and edited the manuscript. TWM and NLM edited the manuscript and contributed to the collection and measurement of the data used. The authors have no conflicts of interest to declare.

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