Postprandial Triglycerides Predict Newborn Fat More Strongly than Glucose in Women with Obesity in Early Pregnancy

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Objective: Maternal obesity (OB) accounts for the majority of large-for-gestational-age infants, and newborn percent fat (NB%fat) correlates strongest with childhood OB. In addition to maternal glucose, fasting triglycerides (TGs) may contribute, but postprandial triglycerides (PPTGs) are unstudied. It was hypothesized that fasting TGs and PPTGs are higher in women with OB compared with women with normal weight (NW) throughout pregnancy, correlate more strongly with NB%fat than glucose, and may relate to dietary chylomicron TGs.

Methods: Fasting TGs and PPTGs, free fatty acids, glucose, and insulin were prospectively measured 10 times over 4 hours after a controlled liquid breakfast early (14-16 weeks) and later (26-28 weeks) in pregnancy in 27 mothers with NW and 27 with OB. NB%fat was measured by dual x-ray absorptometry.

Results: Fasting TGs and PPTGs were already ≥30% higher in mothers with OB at 14 to 16 weeks (P < 0.001) versus mothers with NW. In mothers with OB, a simple 1-hour (r = 0.71; P < 0.01) or 2-hour (r = 0.69; P < 0.01) PPTG at 14 to 16 weeks correlated strongest with NB%fat. In mothers with NW, the increase in TGs from early to later pregnancy correlated strongest with NB%fat (r = 0.57; P < 0.01). Maternal glucose did not statistically add to prediction models.

Conclusions: These novel data suggest that 1- or 2-hour PPTGs might be a new target for early intervention in pregnancies with OB to prevent excess newborn adiposity and attenuate child OB risk.

Introduction

Obesity (OB) affects nearly 40% of women of child-bearing age (1) and accounts for a greater number of large-for-gestational-age (LGA) infants than pregnancies complicated by gestational diabetes mellitus (GDM) (2). The fetal overnutrition hypothesis suggests that maternal fuels contributing to excess fetal growth and childhood OB are not limited to glucose and that these fuels are in greater abundance in maternal OB (3). Our group previously demonstrated that, despite a controlled diet, women with OB had higher 24-hour glycemic patterns than those with normal weight (NW) both early and later in gestation (4), but a single fasting triglyceride (FTG), measured once in early pregnancy, correlated more strongly than glucose with newborn percent fat (NB%fat). Postprandial (PP) lipids were not measured, and NB%fat was estimated by skinfolds. Some studies (4) have shown that FTGs and fasting free fatty acids (FFAs) may contribute to fetal fat accretion, but well-controlled, prospective studies in women with OB have not been performed (5). Furthermore, recent evidence has suggested that early exposure to excess maternal fuels may increase the risk for excess fetal growth equal to or greater than later exposure (6).

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Because of inconsistent data, maternal lipids are not recognized risk factors for excess fetal fat accretion and are not currently targeted for intervention. Whether postprandial triglyceride (PPTG) elevations more strongly contribute to fetal growth requires elucidation (5, 7–12), especially given that PP glucose predicts excess growth and is the standard of care in the management of GDM. Most studies have not controlled for maternal diet, which markedly affects both FTGs and PPTGs for up to 3 days before measurement (13). Moreover, differential lipoprotein contributions to total triglycerides (TGs) from maternal diet (chylomicrons [CM-TGs]) vs. liver-synthesized TGs (very low-density lipoproteins [VLDL-TGs]) are unreported. Both may be important given that TGs are hydrolyzed by placental lipases to FFAs for fetal fat accretion (14). Our group recently demonstrated that the activity of placental lipoprotein lipase was correlated with newborn adiposity (15). If one type of TG lipoprotein correlates more strongly with fetal fat accretion, targeting FTGs (VLDL-TGs) versus PPTGs (CM-TGs) through interventions may be more effective (16). New data have also supported that the early intrauterine metabolic environment may influence placental nutrient transport and fetal growth more than in later pregnancy. This may be, in part, why midgestation interventional trials to prevent LGA infants are often unsuccessful (17). Although birth weight is typically used to quantify growth, NB%fat is a better proxy for intrauterine nutrient exposure and stronger predictor of childhood OB (18). To account for these important factors, we designed a prospective trial that carefully controls maternal diet to test the hypothesis that FTGs and PPTGs are higher in women with OB versus women with NW, both early and later in pregnancy, more strongly predict NB%fat than glucose.

**Methods**

**Study population and design**

This was an NIH-funded prospective trial (R56DK078645; R01DK078645) approved by the Colorado Multiple Institutional Review Board (COMIRB 07-0535). Pregnant women (18–35 years old) were recruited at University of Colorado Hospital from 2008 to 2015. Fifty-four English-speaking mothers with singleton pregnancies who were otherwise healthy were enrolled at ∼12 weeks gestation based on prepregnancy BMI (with NW: n = 27; BMI 20.25 kg/m²; with OB: n = 27; BMI 30.38 kg/m²). All chronic medical conditions were excluded as was a history of preclampsia to minimize the risk of placental insufficiency and growth restriction. Mothers with a history of preterm birth (PTB) were excluded because of the progressive increase in fetal fat accretion from 28 to 40 weeks given that the primary outcome was fat mass in term infants (∼37 weeks) by dual x-ray absorptiometry (DXA). All women with OB were screened for glucose intolerance before enrollment (19) and excluded if they failed an early 100-g oral glucose tolerance test (OGTT) by Carpenter and Coustan criteria (19).

All 27 mothers with NW and 24 out of 27 with OB were studied both early (14–16 weeks) and later (27–28 weeks) in pregnancy for their fasting and PP response to a liquid test meal. Three mothers with OB studied early could not be studied later because of gallbladder disease, pregnancy loss, or relocation. At 28 weeks, all subjects underwent a 100-g OGTT to exclude GDM (19), and subjects had glucose and insulin measured at baseline or fasting and 1, 2, and 3 hours for insulin sensitivity estimates. Given rapid fetal fat accumulation over the third trimester, only term (∼37 weeks), healthy newborns were analyzed for percent fat by DXA. One newborn from a mother with NW was excluded because of PTB. Of the 24 mothers with OB who completed both early and later studies, five newborns could not undergo DXA because of PTB, preterm premature rupture of membranes, preeclampsia, subchorionic hemorrhage, and birth trauma, resulting in 26 offspring with NW and 19 with OB for term NB%fat analysis.

**Liquid meal studies for metabolic measures**

Because diet affects glucose and lipids for several days (13), subjects were provided with 3-day standardized lead-in diets prepared by the Colorado Clinical Translational Science Institute (CCTSI) metabolic kitchen preceding the two liquid breakfast visits. The lead-in and liquid breakfast diets were matched for macronutrients, with 50% carbohydrate (30% complex and 20% simple sugars), 35% fat (12% saturated, 12% monounsaturated, and 11% polyunsaturated), and 15% protein. Energy requirements were based on Institute of Medicine guidelines (with OB: 25 kcal/kg; with NW: 30 kcal/kg). Studies were conducted within tight gestational windows of 14 to 16 and 26 to 28 weeks given the progressive increase in insulin resistance (IR) during pregnancy.

After 3 days of standardized diet at 14 to 16 weeks and 26 to 28 weeks, fasted subjects (10 h) had baseline labs drawn at the CCTSI. They were then given a liquid breakfast shake (30% of total calories) based on data that the PPTG response can be completely captured within 4 hours after a liquid breakfast (20). Following breakfast, nine additional samples were collected over 4 hours (20, 40, 60, 90, 120, 150, 180, 210, and 240 min) for plasma TGs, glucose, insulin, and

| Table 1 Maternal and newborn characteristics of subjects with NW and OB |
|--------------------------------|-------------------|-------------------|
| **Maternal characteristics** | NW (n = 27) | OB (n = 27) |
| **Age (y)** | 30.5 ± 0.63 | 29.8 ± 0.80 |
| **Prepregnancy BMI (kg/m²)** | 22.3 ± 0.34 | 31.7 ± 0.62a |
| **Gestational weight gain (kg)** | 13.7 ± 0.84 | 14.2 ± 1.6 |
| **Primigravida (%) total** | 14 (51.9) | 11 (40.7) |
| **White (%) total** | 25 (92.6) | 25 (92.6) |

| **Newborn characteristics** | NW (n = 26) | OB (n = 19) |
|----------------------------|-------------|-------------|
| **Gestational age at delivery (wk)** | 39.7 ± 0.2 | 39.7 ± 0.23 |
| **Cesarean (%) total** | 23% | 37% |
| **Birth weight (g)** | 3,258.0 ± 73.6 | 3,557.6 ± 107.8a |
| **Female (%) total** | 50% | 32% |
| **2-wk NB%fat** | 8.9 ± 0.72 | 11.0 ± 1.2 |
| **2-wk total mass (g)** | 3,864.8 ± 95.4 | 4,122.5 ± 136.9 |

Data are mean ± SEM. aIndicates NW vs. OB, P < 0.004. NB%fat, newborn percent fat.
FFAs (CCTSI laboratory) using assays previously reported (4,21). Using the trapezoidal method, the 4-hour area under the curve (AUC) was calculated to characterize the PP glucose, insulin, TG, and FFA response to the meal (21). To determine whether the 4-hour AUC correlated with simpler 1-hour or 2-hour PP measures, similar to those used in GDM to capture PP glucose responses, the 4-hour TG-AUC and 4-hour glucose AUC were correlated with the 1-hour and 2-hour PPTGs and PP glucose. Because maternal IR increases availability of all nutrients to the fetal-placental unit, maternal IR was estimated by the following three indices: (1) fasting IR by homeostatic model assessment of IR (22), (2) PP IR by 4-hour glucose and insulin AUC product (Meal-IR; glucose AUC × insulin AUC), and (3) OGTT-IR glucose and insulin AUC product (OGTT; glucose AUC × insulin AUC) (23) on the 28-week, 3-hour 100-g OGTT. Using the trapezoidal method, the 4-hour area under the curve (AUC) (23) on the 28-week, 3-hour 100-g OGTT.

**Table 2** Metabolic measures early (12-14 wk) and later (26-28 wk) in gestation between women with NW and OB

|                  | NW Early (n = 27) | NW Later (n = 27) | Delta        | OB Early (n = 27) | OB Later (n = 24) | Delta        |
|------------------|------------------|------------------|--------------|------------------|------------------|--------------|
| FTG (mg/dL)      | 89.2 ± 3.98      | 135.1 ± 7.8      | 45.9 ± 5.3   | 126.2 ± 8.7a     | 174.9 ± 12.2b    | 50.2 ± 5.9   |
| 1-h PPTG (mg/dL) | 95.3 ± 4.6       | 153.2 ± 8.0      | 58.0 ± 4.6   | 143.4 ± 10.8b    | 201.2 ± 13.3b    | 60.1 ± 6.0   |
| 2-h PPTG (mg/dL) | 86.6 ± 5.2       | 137.9 ± 8.1      | 51.3 ± 5.1   | 135.3 ± 10.7a    | 189.1 ± 13.1a    | 55.9 ± 6.4   |
| TG-AUC (mg × min/dL) | 22708.7 ± 1216.4 | 34,467.6 ± 1,879.9 | 11,758.9 ± 1,005.7 | 33,584.6 ± 2,629.2 | 46,209.2 ± 3,245.5 | 132,441.1 ± 481.1 |
| Fasting glucose (mg/dL) | 73.0 ± 0.88       | 72.7 ± 1.13      | -0.37 ± 0.94 | 76.7 ± 0.99b     | 76.9 ± 1.1b  | 0.25 ± 1.32  |
| 1-h PP glucose (mg/dL) | 83.3 ± 2.5        | 83.6 ± 2.5       | 0.26 ± 2.4  | 90.3 ± 2.5a      | 96.3 ± 2.9b    | 5.1 ± 2.8    |
| 2-h PP glucose (mg/dL) | 85.6 ± 1.6        | 86.6 ± 1.9       | 1.1 ± 1.7   | 93.2 ± 1.5a      | 95.5 ± 1.7b    | 2.1 ± 1.9    |
| Glucose-AUC (mg × min/dL) | 19,513.9 ± 255.3 | 19,472.2 ± 331.5 | -41.7 ± 230.6 | 21,280.6 ± 337.8a | 21,629.6 ± 281.9a | 379.1 ± 433.3 |
| Fasting insulin (μIU/mL) | 6.6 ± 0.6 n = 27  | 9.1 ± 0.73       | 2.5 ± 0.62  | 10.5 ± 1.2b      | 13.7 ± 1.4b    | 3.0 ± 0.96   |
| 1-h PP insulin (μIU/mL) | 37.9 ± 4.2        | 48.6 ± 4.8       | 10.8 ± 4.0  | 62.2 ± 9.4c      | 85.0 ± 11.1b  | 22.5 ± 5.5   |
| Insulin-AUC (μIU × min/mL) | 4,995.9 ± 408.9  | 6539.4 ± 430.9   | 1,543.5 ± 291.9 | 9,423.3 ± 132.3a | 12,766.7 ± 1,673.2a | 3328.0 ± 596.2 |
| Fasting FFA (μEq/L) | 665.2 ± 30.5      | 502.96 ± 96      | -152.2 ± 34.0 | 628.8 ± 42.7     | 557.42 ± 30.2  | -49.3 ± 33.0 |
| FFA-AUC (μEq × min/L) | 68,017.6 ± 2,343.4 | 64,410.2 ± 2,834.8 | -3,607.4 ± 2,685.9 | 67,548.3 ± 4,784.9 | 65,942.1 ± 3,188.5 | -1,880.7 ± 2,758.3 |
| HOMA-IR | 1.2 ± 0.12 | 1.7 ± 0.15 | 0.47 ± 0.12 | 2.02 ± 0.25b  | 2.6 ± 0.29b | 0.59 ± 0.2b |
| Meal-IR (× 10^7) | 9.9 ± 0.89 | 13.0 ± 1.0 | 3.1 ± 0.69 | 20.6 ± 3.3b | 28.2 ± 4.1a | 7.61 ± 1.54b |
| OGTT-IR (× 10^8) | 2.4 ± 0.33 | 2.4 ± 0.33 | 0.0 ± 0.00 | 3.96 ± 0.48b | 3.96 ± 0.48b | 0.0 ± 0.00 |

Data are mean ± SEM. 
*Indicates NW vs. OB at same time point, P < 0.001.
**Indicates NW vs. OB at same time point, P < 0.01.
***Indicates NW vs. OB at same time point, P < 0.05.
AUC: area under the curve; IR: insulin resistance; OGTT, oral glucose tolerance test; PPTG, postprandial triglycerides; FTG, fasting triglycerides; FFA, free fatty acids; HOMA-IR, homeostatic model assessment of IR.

Total FTGs and PPTGs were separated to measure TG-rich lipoproteins synthesized from the liver (VLDL-TGs) versus dietary chylomicrons from the gut (CM-TGs) given that both can be hydrolyzed by placental lipoprotein lipase (14) into FFAs for fetal fat accretion. TG-rich lipoprotein separations were performed successfully as previously described (24) from samples collected (0, 60, 120, 180, and 240 minutes) in 33 women.

**Newborn fat measures**

Forty-five term newborns underwent DXA at Children’s Hospital Colorado at ~2 weeks of life (mean 15.6 days old; range 12-20 days old) (QDR Discovery fan beam densitometer with Apex software version 3.2, Hologic Delphi-W; Hologic, Inc., Marlborough, Massachusetts) as described previously (25) for measurement of fat mass and fat-free mass. The DXA was performed at 2 weeks because of the expected newborn diuresis affecting total body water and the reequilibration of fat mass by 7 to 14 days (26), especially in breastfed infants. Later in the study, air displacement plethysmography (PEA POD; COSMED, Rome, Italy) was added (same day ± 2 hours of DXA) to also estimate NB%fat because of scanning ease (25) and absence of any radiation; however, because it was unavailable for the first third of the cohort, %fat by DXA is reported. In two newborns (one from mother with NW and one from mother with OB), DXA revealed a calibration error. Given that our previous data (25) showed a strong correlation between 2-week DXA and PEA POD (r = 0.74), both were used (n = 33 paired cases) to determine a regression allowing prediction of NB%fat by DXA “y” using the PEA POD estimate “x” (y = 0.77x + 1.35) in the two cases of DXA calibration error.

**Statistical analysis**

Data are mean ± SEM; all approximated a normal distribution. Between-group differences were assessed using t tests for independent groups, and within-group differences were assessed by paired t tests. Correlations were assessed using Pearson’s r. Variables that exhibited univariate significance were included in simple and multiple linear regression models to test for predictive associations (SPSS version 24; IBM Corp., Armonk, New York). Power was calculated a priori (PASS Software; Kaysville, Utah) to test the hypothesis that mothers with OB have higher FTGs in early and later gestation.
Based on pilot data (R56DK078645), 15 women per group would detect an FTG difference of 58 mg/dL (SD = 34.12) for 97% power (\( \alpha = 0.017 \)) using a two-sided/two-sample \( t \)-test. Furthermore, it was calculated a priori from our pilot data (\( R^2 = 0.81 \); two-sided) that a total of 45 women would allow for > 80% power (\( \alpha = 0.05 \)) to detect a significant association between the change in FTGs from early to late pregnancy and NB%fat. A Bonferroni correction was applied to minimize the risk of a type I error from multiple comparisons; \( \alpha \leq 0.01 \) was considered statistically significant.

Results

Maternal and newborn characteristics

Age, gestational weight gain, and percent primigravidas were not statistically different between groups; 93% were white (Table 1). By design, the mean prepregnancy BMI in women with NW was 22.3 versus 31.7 in women with OB; gestational age at delivery was identical. A slightly higher percentage of males were born to women with OB compared with women with NW (68% vs. 50%; \( P > 0.05 \)). Birth weight was significantly higher in offspring from mothers with OB, with a trend for increased NB%fat. All except one infant in each group were exclusively breastfed.

Metabolic differences between groups

Table 2 and Figure 1 show that FTGs were higher in OB, early and later, as were fasting insulin, glucose, and the 1- and 2-hour PP and 4-hour AUC measures. Fasting glucose was < 80 mg/dL, early and later in both groups, indicative of relatively healthy women with OB, and glucose were overall ~10% higher in the mothers with OB. More striking than differences in glucose were the 30% to 40% differences in FTGs, 1-hour and 2-hour PPTGs, and the 4-hour TG-AUC (OB vs. NW FTGs: 126.2 vs. 89.2 mg/dL, early; 174.9 vs. 135.1 mg/dL, later; both \( P < 0.01 \)). The change from early to late gestation between groups did not differ. Women with OB had 50% to 60% higher fasting and PP insulin (Figure 1B), and they demonstrated greater IR by all estimates both early and later (\( P < 0.01 \); Table 2). In fact, insulin and glucose were already higher in early pregnancy in women with OB compared with women later in pregnancy with NW (Figure 1B-1C).

Later in pregnancy, women with OB had the highest total TGs (including CM-TGs and VLDL-TGs; Figure 1A) in the fasting and PP states. Importantly, early-pregnancy TGs in women with OB were already as high as later TGs in women with NW. PPTGs peaked 1 hour after the meal, and the increase in 1-hour PPTGs in the total cohort was accounted for by both dietary CM-TGs (\( r = 0.91 \); \( P < 0.001 \)) and VLDL-TGs (\( r = 0.78 \); \( P < 0.01 \)). We further determined that the 4-hour TG-AUC could be entirely captured by a single 1-hour PPTG or 2-hour PPTG (both \( r = 0.98 \); \( P < 0.001 \)). We emphasize the 1-hour PPTG measure for simplicity. PP FFAs were not different between the groups (Figure 1D) and were similarly suppressed by the much higher insulin levels in women with OB.

Predictors of newborn adiposity

Table 3 and Figures 2–5 show correlations and simple and multiple regressions for TGs and glucose with NB%fat, early, later, and by group. In the total cohort (Figure 2), FTGs early and later similarly correlated with NB%fat (\( r = 0.47 \), early; \( r = 0.56 \), later; both \( P \leq 0.001 \)), as did 1-hour and 2-hour PPTGs (\( r = 0.57 \), early; \( r = 0.54-0.58 \), later; both \( P < 0.001 \)), and they predicted ~32% of the variance in NB%fat (\( R^2 = 0.32 \); \( P < 0.001 \)). The TG lipoprotein fractionations in 33 out of 45 mothers revealed that, in the total cohort, early 1-hour CM-TGs significantly correlated with NB%fat (\( r = 0.61 \)), as did 1-hour VLDL-TGs (\( r = 0.59 \)). In mothers with OB

\[ \text{NB%fat} = a_0 + a_1 \times \text{FTG} + a_2 \times \text{Insulin} + a_3 \times \text{Glucose} + a_4 \times \text{TG-AUC} \]
(Figure 3), FTGs in early pregnancy (r = 0.60; P = 0.006) obtained at 14 to 16 weeks correlated more strongly with NB%fat than later FTGs (r = 0.55; P = 0.01) obtained at 26 to 28 weeks. Notably, the early 1-hour PPTGs (r = 0.71; P = 0.001; Figure 3C) most strongly correlated with NB%fat compared with later 1-hour PPTGs (r = 0.63; P = 0.004; Figure 3D). In fact, in mothers with OB, the early 1-hour or 2-hour PPTG predicted ~50% of the variance of NB%fat (R² = 0.50; P < 0.01). In contrast to mothers with OB,
among mothers with NW (Figure 4), the increase (delta) in FTGs from early to later pregnancy ($r = 0.59; P = 0.001$) as well as later FTGs ($r = 0.48; P \leq 0.01$) correlated with NB%fat. Similarly, the increase in total TG-AUC from early to later ($r = 0.57; P = 0.002$), as well as later TG-AUC ($r = 0.44; P = 0.02$), was correlated with NB%fat. The early to later changes in FTGs and PPTGs predicted a similar variance in NB%fat ($R^2 = 0.32-0.35; P \leq 0.01$) in mothers with NW. Unlike mothers with OB, there were no significant predictions in mothers with NW between early FTGs or early PPTGs and NB%fat (Table 3).

Compared with FTGs, fasting glucose was not correlated with NB%fat in the total cohort or by group (Table 3). However, in the total cohort, both the early and later 4-hour glucose AUC was correlated with NB%fat ($r = 0.43$, early; $r = 0.42$, later; both $P \leq 0.01$; Figure 5A-5B), as was the 2-hour PP glucose ($r = 0.40$, early; $r = 0.43$, later; both $P < 0.01$).
These glucose correlations were driven by mothers with OB given that the early and later 4-hour glucose AUC significantly correlated with NB%fat in mothers with OB (r = 0.54 and r = 0.47, respectively; P < 0.05; Figure 5C-5D) but not in mothers with NW.

As specified in our sample size calculation, we used linear regression to determine the influence of TGs or other measures on the prediction of NB%fat. Whereas the early 1-hour PPTGs were most predictive of NB%fat in mothers with OB (R² = 0.50; Table 3), glucose AUC did not significantly add to predictions (all P > 0.05), nor did maternal BMI. Insulin, IR estimates, or FFAs did not correlate with NB%fat in the total cohort or by group. Although there were strong correlations between TG measures and NB%fat, there were no significant correlations with birth weight.

**Figure 4** In women with NW, the change (delta) in (A) FTGs from 12 to 14 weeks to 26 to 28 weeks, (B) later-gestation FTGs, (C) total TG-AUC from 12 to 14 weeks to 26 to 28 weeks gestation, and (D) later-gestation TG-AUC were strongly predictive of NB%fat (Δ = change).

**Figure 5** Across the total cohort, (A) early 4-hour glucose AUC was similarly predictive of NB%fat compared with the (B) later 4-hour glucose AUC. In women with OB (but not with NW), the 4-hour glucose AUC was also modestly predictive of NB%fat both (C) early and (D) later in gestation.
Discussion

To our knowledge, this study is the first to demonstrate that women with OB have substantially higher FTGs and PPTGs compared with women with NW both early and later in pregnancy, despite a controlled diet. The PPTG response was explained by both dietary CM-TGs and VLDL-TGs. Highly relevant to clinical practice, a single 1-hour or 2-hour PPTG in pregnancy captured the entire 4-hour TG-AUC meal response. Surprisingly, in mothers with OB, the early 14- to 16-week 1-hour PPTGs correlated most strongly with NB%fat (r = 0.71; P = 0.001). NB%fat was not correlated with fasting glucose in any group, and only the 4-hour glucose AUC or 2-hour PP glucose correlated modestly in mothers with OB (Table 3). Together, these data suggest that FTGs and, more importantly, PPTGs may be under-recognized important contributers to fetal fat accretion, particularly in glucose-tolerant mothers with OB. Most striking in women with OB, the prediction between maternal TGs and NB%fat was strongest early in pregnancy, related to both CM-TGs and VLDL-TGs, and captured by 1- or 2-hour PPTG.

The American College of Obstetricians and Gynecologists identified maternal OB as the greatest public health risk in pregnancy, and the largest number of LGA infants are born to mothers with OB (2). The intrauterine environment in OB is characterized by nutrient excess and is associated with an increased risk for childhood OB (20% of preschoolers) (27), glucose intolerance, and nonalcoholic fatty liver disease, the latter occurring in ~40% of children with OB and the leading cause of liver transplantation (28). Offspring from women with OB or GDM are born with increased subcutaneous fat (29). We have shown by magnetic resonance imaging spectroscopy that these 2-week-old newborns already had 68% more intrahepatic fat compared with newborns of mothers with NW (30), potentially a risk factor for the subsequent development of nonalcoholic fatty liver disease. Offspring OB risk was shown to be best predicted by maternal OB more so than GDM in a cohort of offspring who had a birth fat mass measured by DXA at 9 years of age (18). Furthermore, fat mass at birth, not birth weight, predicted fat mass at 9 years, supporting that NB%fat is a better predictor of childhood OB (18).

Investigators have sought to determine whether glucose, lipids, or excess gestational weight gain may be driving the risk of excess fetal growth in maternal OB (31). We show that, despite similar weight gain (Table 1), both FTGs and PPTGs were ~30% to 40% higher over gestation in mothers with OB, and early 1-hour PPTGs (similar to 2-hour PPTGs) most strongly predicted NB%fat (R² = 0.50; P < 0.01), accounting for 50% of the variance. Studies have inconsistently shown a correlation between FFAs or FTGs and fetal growth (4,5,7-9), but PPTGs are rarely measured. Placental lipid metabolism and transport play a central role in determining fetal FFA availability, which is complex. Our group has shown that the activity of placental lipoprotein lipase, which hydrolyzes maternal TGs to FFAs for fetal-placental availability, was correlated with NB%fat estimated by skinfolds at birth (15). The inconsistency in trials exploring maternal TGs and fetal growth may not be only because of absent newborn fat mass measurements, but also because of the influence of maternal diet on TGs. Diet influences FTGs by ~20% for up to 3 days before sampling (13). We therefore provided a eucaloric diet with an identical macronutrient composition to isolate the effect of maternal OB from diet on maternal lipid and glucose metabolism. We demonstrated that fasting and PP insulin concentrations were already impressively ~50% higher in mothers with OB versus those with NW in early pregnancy (Table 2). Mothers with OB also had higher IR entering gestation, previously shown by preconception insulin clamp data (32). Maternal IR in OB increases maternal lipolysis, elevating FTGs and FFAs (31,33). Because the fetus has a limited capacity for de novo lipogenesis and fatty acid oxidation, excess maternal TGs can be hydrolyzed to FFAs by placental lipases for fetal fat accretion (14,33-35). Although the high insulin levels generated by women with OB suppressed PP FFAs to levels similar to those in women with NW, the early FTGs and PPTGs in women with OB were already as high as those in mothers with NW later in pregnancy (Figure 1A), providing early fetal-placental exposure to excess lipids (36).

The 50% to 60% higher fasting insulin concentrations in mothers with OB suppressed fasting glucose to only slightly higher than that in mothers with NW (Table 2), and this may be why, in part, fasting glucose did not correlate with NB%fat. However, the 4-hour glucose AUC, which better captures the entire glucose exposure, was ~10% higher in mothers with OB early and later compared with that in mothers with NW (Figure 1C), and the 4-hour glucose AUC early and later were modestly correlated with NB%fat in mothers with OB but not in mothers with NW (Table 3). This is consistent with our previous study (4), in which mothers with OB had ~8% higher 24-hour glucose profiles by continuous glucose monitoring early and later, but a single early FTG was more strongly correlated with NB%fat.

There is a growing recognition of the importance of early excessnutrient transport, shifting the focus to earlier or prepregnancy interventions (6,17,31,33) to decrease LGA rates. This earlier focus has also been suggested by the disappointing outcomes with later-pregnancy interventions and by data supporting that early fetal hyperinsulinemia drives fetal growth (6). Our data strongly support this focus, especially in pregnancies with OB. Although the increase in PPTGs from early to late pregnancy in mothers with NW was more strongly predicted NB%fat, the strongest predictor was the early 1-hour PPTGs in women with OB. This suggests that, over the course of pregnancy, TG increases in women with NW contribute to fetal fat accretion. However, in women with OB, TGs are already high in early pregnancy and strongly relate to infant adiposity, suggesting that interventions to reduce them must occur early, or perhaps even prepregnancy.

Limitations include that this was primarily a white cohort, and findings may be different in other ethnicities. Furthermore, risk factors for preeclampsia or preterm delivery were excluded because they could confound NB%fat measures given that fetal fat accretion continues at ~0.1% per day until 40 weeks of gestation (37,38). Except for higher IR and TGs, this cohort with OB was relatively healthy, as demonstrated by the low glucose. Generalizability to less healthy populations with OB is limited. Despite enrolling relatively healthy women with OB, 19 out of 27 newborns from the group with OB were evaluable by DXA because of obstetric complications or delivery < 37 weeks. This underscores the increased risk of adverse outcomes in women with OB without risk factors for preterm delivery or preeclampsia. With a larger sample size, glucose may be found to independently contribute to a prediction model in mothers with OB. The analysis of newborn sex differences between groups was limited by power. Although the 1-hour PPTG correlation with NB%fat in the pooled cohort was strongest for males (r = 0.68, early; r = 0.59, later) versus females (r = 0.43, early; r = 0.49, later),
we are unable to draw conclusions of significance given that we were not powered to detect sex differences. Lastly, female newborns have slightly more NB%fat than males (37). Although more male offspring were delivered from mothers with OB, adjustment for sex showed that the effect between sex and groups was of borderline significance (P = 0.1), suggesting that the lack of a statistically significant difference in NB%fat between groups was also likely because of the limited sample size.

Conclusion

Going forward, the clinical implication of these findings is that measuring 1- or 2-hour PPTG after a meal, similar to 1- or 2-hour PP glucose typically measured in GDM, may identify an important metabolic contributor to newborn adiposity previously unrecognized. Given that the 1- and 2-hour PPTGs were correlated strongest with NB%fat, these data suggest that the maternal TG response to diet might be targeted and lowered by a dietary intervention and/or omega-3 fatty acid supplements, especially in those with higher TG levels. In women with OB, interventions should be targeted <14 weeks or preconception and, if proven successful in a future randomized controlled trial, could represent a paradigm shift in focus and management. Our mothers ingested a healthy diet prior to the studies. How a fast-food diet, higher in saturated fat and simple carbohydrates, is likely to further increase PPTGs and impact newborn adiposity remains to be studied in a real-world environment. Discerning whether this PPTG association occurs in GDM, for which the focus of treatment has primarily been glucose lowering, deserves further study given the persistently high LGA rate. Because portable point-of-care lipid testing that uses meters similar to the size of glucometers is becoming more affordable and precise (39,40), obtaining repeated FTG and PPTG measures in a larger population of women at risk for fetal overgrowth is feasible and should be done to confirm these associations. Current glucose-centered strategies are only partially effective. With an ever-growing maternal OB epidemic accompanied by an increase in LGA infants, novel approaches that target excess fetal growth earlier in pregnancy to attenuate risk for childhood metabolic disease are merited.

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