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# Maternal Serum Lipids During Pregnancy and Infant Birth Weight: The Influence of Prepregnancy BMI

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**Maternal obesity may be associated with metabolic factors that affect the intrauterine environment, fetal growth, and the offspring's long-term risk for chronic disease. Among these factors, maternal serum lipids play a particularly important role. Our objective was to estimate the influence of variation in maternal serum lipid levels on variation in infant birth weight (BW) in overweight/obese and normal weight women. In a prospective cohort of 143 gravidas, we measured maternal serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) at 6–10, 10–14, 16–20, 22–26, and 32–36 weeks gestation. Effects of maternal serum lipid levels on infant BW adjusted for gestational age at delivery (aBW) were analyzed using linear regression models. In analyses stratified by maternal prepregnancy BMI categorized as normal (≤25.0 kg/m$^2$) and overweight/obese (>25.0 kg/m$^2$), we found a significant ($P < 0.05$) inverse association between aBW and HDL-C at all time points starting at 10 weeks gestation in overweight/obese women. No significant effect was found in normal weight women. In contrast, increased maternal serum TG was significantly associated with increased aBW only for normal weight women at 10–14 and 22–26 weeks gestation. Variation in aBW is not associated with variation in maternal serum TC or LDL-C for either stratum at any time point. We postulate that such differences may be involved in the "physiological programming" that influences later risk of chronic disease in the infants of overweight/obese mothers.**

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## INTRODUCTION

Maternal obesity may be associated with metabolic factors that affect the intrauterine environment, fetal growth, and the offspring's long-term risk for chronic disease (1,2). However, the physiologic pathways mediating the effects of maternal obesity are not well characterized. Changes in maternal lipid metabolism are a normal physiologic response to pregnancy. Progressive increases of circulating lipids, which optimize the availability of substrates necessary for fetal growth and development (3–6), have been consistently demonstrated to influence the intrauterine environment and fetal outcomes. There is growing evidence that obese individuals may exhibit distinct metabolic patterns that may influence lipid homeostasis and the development of many of the pathological conditions associated with obesity (7–9). We have recently shown that such metabolic differences may be associated with differences in maternal lipid profiles during pregnancy (10). However, few studies have documented how differences in the metabolic response of obese mothers may affect the relationship between maternal lipids and fetal growth and development.

In cross-sectional studies, maternal serum triglyceride (TG) levels in mid to late second trimester are positively associated with birth weight (BW) after adjusting for maternal BMI (11–13); likewise, decreased levels of maternal total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) have been associated with intrauterine growth restriction (5). Case–control studies have also reported inverse associations between maternal high-density lipoprotein cholesterol (HDL-C) levels and risk of macrosomia (5,12,14,15). In addition to influencing fetal growth, such metabolic factors may also result in fetal responses that have long-term health consequences; for example, maternal hypercholesterolemia has been linked to increased cholesterol deposition in the fetal aorta that may influence risk of long-term morbidity (16). However, these studies do not directly address the possibility that the distinct metabolic patterns found in obese and nonobese women may result in qualitatively different effects on the growing fetus.

The goal of this study was to estimate the influence of variation in maternal lipid levels during pregnancy on variation in infant BW in women with overweight/obese prepregnancy

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BMI (>25.0) and normal prepregnancy BMI (≤25.0). We specifically monitored these women at multiple time points across gestation in order to gain insight into the influence of longitudinal variation in lipid levels on infant BW.

## METHODS AND PROCEDURES

### Study sample

We recruited 152 participants as part of an ongoing prospective cohort study of pregnant women at the University of Michigan Health System (Ann Arbor, MI). The institutional review board of the University of Michigan Medical School (Ann Arbor, MI) approved the study protocols. Eligible participants were 18–45 years of age, between 6 and 10 weeks gestation with a singleton pregnancy, and intended to deliver at the study hospital. Informed consent was obtained at the initial visit. Data and laboratory samples were collected at five time points during pregnancy: 6–10, 10–14, 16–20, 22–26, and 32–36 weeks gestation. At each time point, we obtained data from a brief interview, maternal anthropometric measurements, fetal ultrasound measurements, and maternal blood draw. Data analyses were carried out on the cohort of 143 participants who completed the study and delivered a live infant. Fewer than 1% of women were excluded from any particular analysis because of missing data.

### Data collection and variables

Baseline maternal demographic and health characteristics were collected by questionnaire upon entry into the study as well as subsequent review of medical records. Changes in maternal health characteristics were assessed at each subsequent time point. Standing height was measured at the baseline visit using a wall-mounted stadiometer. Weight was measured at each time point in light street clothes, without shoes, on a calibrated electronic scale (Scale-tronix, White Plains, NY). Maternal prepregnancy weight was collected by self-report at the initial visit. Prepregnancy BMI was calculated using height and prepregnancy weight (BMI = weight/height (2)), and categorized into two levels using World Health Organization cutoff points as normal weight (≤25.0 kg/m$^2$) and overweight/obese (>25.0 kg/m$^2$) based on the most recent recommendations of the Institute of Medicine (17).

At each time point, maternal venous blood from nonfasting participants was collected in a standard serum separator tube and allowed to clot for 30 min before centrifugation for 15 min at 1,000*g*. While the use of nonfasting blood samples may lead to greater variation in lipid levels, particularly TG, previous research has shown that it is unlikely to introduce systematic bias, either across time or between BMI categories that would alter the associations reported here. Prior studies of nonpregnant adults have shown that lipid profiles change only minimally in response to food intake (18), show high correlations between fasting and postprandial levels (19) and are similarly associated with disease risk in both the fasting and nonfasting state (18,20,21). Accordingly, in pregnant women, at least one prior study has shown that plasma lipids do not appreciably change with time after a meal (22). In addition, nonfasting samples are significantly associated with pregnancy outcomes consistent with studies using fasting blood samples to determine lipid concentrations (15,22,23).

Serum was immediately aliquotted and stored at −20 °C. Quantitative lipid assays were performed in the Chemistry Laboratory of the Michigan Diabetes Research and Training Center using standard methods. Serum TC was enzymatically determined using reagent for cholesterol (no. 3313018; Roche Diagnostics, Indianapolis, IN). Serum TG was measured using a colorimetric enzymatic assay (no. 3034658; Roche Diagnostics). Serum LDL-C was measured using the LDL Direct Liquid Select system (no. 7120; Equal Diagnostics, Exton, PA). HDL-C was measured directly using the HDL Direct reagent (no. 3034569; Roche Diagnostics).

Infant variables, including date of delivery, BW, and gender, were collected at delivery. An ultrasound estimate of gestational age was determined by early first trimester ultrasound. Since BW varies significantly with gestational age, the BW was regressed onto gestational age. The residual values from each fit were used to represent the gestational age–adjusted BW (aBW). These residuals were then used as the dependent variable for the modeling of the relationship of aBW to maternal serum lipids as described below.

### Statistical analysis

All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Univariate regression models were used to describe the demographic characteristics of the study sample and tested the hypothesis of homogeneity of the means between BMI categories. The Fisher exact test was used to assess statistical significance of categorical variables; the *t*-test was used for continuous variables. We then tested the hypothesis that variation in aBW is not influenced by variation in lipid levels measured at each time point for each BMI category. Univariate and multivariable regression analyses were used to model the cross-sectional relationship between aBW and maternal lipid levels at each time point. Analyses were stratified on maternal prepregnancy BMI as noted above. A *P* value of <0.05 was considered significant. We used a standard longitudinal analytic approach to estimate the effect of repeated measures of maternal serum lipid levels across time on an outcome (aBW) measured at one time point using the following model (24):

$$E(aBW) = \beta' + (\beta_0 + \beta_2 + \beta_4)\, L_0 + (\beta_0 + \beta_2)\, L_{02} + (\beta_2 + \beta_4)\, L_{24} + \varepsilon \quad (1)$$

In this equation, $L_0$ is the baseline lipid level (6–10 weeks gestation); $L_{02}$ is the rate of change of the lipid level during the first half of pregnancy (between the first and third time points) defined as $L_{02} = (L_2 - L_0)/(GA_2 - GA_0)$, where GA is the gestational age in fractions of weeks at time of measurement; and $L_{24}$ is the rate of change of the lipid level in the second half of pregnancy (between the third and fifth time points). As described elsewhere (24), the coefficient for $L_0$ $(\beta_0 + \beta_2 + \beta_4)$ defines the effect of increasing the lipid level by one unit at any study visit. As such, this coefficient describes, for example, the effect of uniformly shifting the trajectory upward across all study visits resulting in a cumulative effect on aBW. The coefficients for $L_{02}$ $(\beta_0 + \beta_2)$ and $L_{24}$ $(\beta_2 + \beta_4)$ define how variation in the rate of weight gain in each visit interval may affect variation in aBW.

## RESULTS

Table 1 presents the sociodemographic and health characteristics of the participants and their newborns. These descriptors are stratified on maternal prepregnancy BMI categorized as normal weight (≤25.0 kg/m$^2$) and overweight/obese (>25.0 kg/m$^2$). While our sample is very homogeneous with regard to measures of socioeconomic status and race, there was considerable variation in prepregnancy BMI. There was a low rate of maternal complications, with only one case of confirmed pregnancy-induced hypertension and 13 cases of gestational diabetes. There were significant demographic differences in women with nonoverweight BMIs compared to those with overweight/obese BMIs, including race, age, education, and income. Notably, however, controlling for these factors did not significantly change our results below (analyses not shown). As expected, the infants of overweight/obese mothers had a significantly higher BW than infants of normal weight mothers (Table 1).

Table 2 gives the results of cross-sectional analyses describing the relationship of aBW to maternal serum lipid levels at five time points spanning pregnancy (6–10, 10–14, 16–20, 22–26, and 32–36 weeks gestation). These analyses are stratified on maternal prepregnancy BMI. We find that the relationships of aBW to maternal HDL-C and TG differ between these two strata. For obese/overweight women, aBW is inversely associated with maternal HDL-C

**Table 1 Characteristics of the study sample**

| | Maternal prepregnancy BMI[a] | | | |
|---|---|---|---|---|
| | All | Normal weight | Overweight/Obese | |
| | | *N* (%) | | *P* value[b] |
| Sample size | 143 | 72 (50.4) | 71 (49.6) | |
| *Maternal characteristics* | | | | |
| Race[b] | | | | |
| White | 115 (80.4) | 61 (84.7) | 54 (76.1) | 0.0161 |
| African American | 11 (7.7) | 2 (2.8) | 9 (12.7) | |
| Asian | 7 (4.9) | 6 (8.3) | 1 (1.4) | |
| Other | 10 (7.0) | 3 (4.2) | 7 (9.8) | |
| Ethnicity | | | | |
| Non-Hispanic | 137 (95.8) | 71 (98.6) | 66 (93.0) | 0.1158 |
| Hispanic | 6 (4.2) | 1 (1.4) | 5 (7.0) | |
| Maternal age[b] | | | | |
| ≤30 | 79 (55.2) | 33 (45.8) | 46 (64.8) | 0.0289 |
| >30 | 64 (44.8) | 39 (54.2) | 25 (35.2) | |
| Parity | | | | |
| Nulliparous | 54 (37.8) | 30 (41.7) | 24 (33.8) | 0.3895 |
| Multiparous | 89 (62.2) | 42 (58.3) | 47 (66.2) | |
| Marital status | | | | |
| Married | 118 (82.5) | 62 (86.1) | 56 (78.9) | 0.2786 |
| Not married | 25 (17.5) | 10 (13.9) | 15 (21.1) | |
| Highest educational level completed[b] | | | | |
| College or less | 85 (59.4) | 35 (48.6) | 50 (70.4) | 0.0105 |
| Postgraduate | 58 (40.6) | 37 (51.4) | 21 (29.6) | |
| Income[b] | | | | |
| ≤$80,000 per year | 72 (50.3) | 29 (40.3) | 43 (60.6) | 0.0127 |
| >$80,000 per year | 70 (49.0) | 43 (59.7) | 27 (38.0) | |
| Missing | 1 (0.7) | — | 1 (1.4) | |
| Insurance | | | | |
| Private insurance | 125 (87.4) | 64 (88.9) | 61 (85.9) | 0.6234 |
| Medicaid/Medicare | 18 (12.6) | 8 (11.1) | 10 (14.1) | |
| Smoking | | | | |
| Not during pregnancy | 132 (92.3) | 66 (91.7) | 66 (93.0) | 1.0000 |
| During pregnancy | 11 (7.7) | 6 (8.3) | 5 (7.0) | |
| *Infant characteristics* | | | | |
| Gender (*N*, %) | 73 (51.0) | 38 (52.8) | 35 (49.3) | 0.7390 |
| Male | 70 (49.0) | 34 (47.2) | 36 (50.7) | |
| Female | | | | |
| Gestational age at birth (days) (mean ± s.d.) | 274.0 ± 13.2 | 273.0 ± 16.1 | 274.9 ± 9.5 | 0.4097 |
| Birth weight (g) (mean ± s.d.)[b] | 3,442.8 ± 543.3 | 3,324.8 ± 564.0 | 3,562.6 ± 497.3 | 0.0084 |

[a]BMI categorized as normal weight (≤25.0 kg/m$^2$) and overweight/obese (>25.0 kg/m$^2$) as described in text. [b]Statistical significance of difference between maternal BMI categories using the student *t*-test for continuous variables and the Fisher exact test for categorical variables.

concentrations at all time points starting at 10 weeks gestation. For normal weight women, aBW is not significantly associated with maternal HDL-C at any visit. Also shown in Table 2, increased maternal serum TG is significantly associated with increased aBW for normal weight women at 10–14 and 22–26 weeks gestation. The effect size is similar

**Table 2 The relationship of gestational age–adjusted birth weight (g) to maternal serum lipid levels (mg/dl) across pregnancy**

| | β (95% CI) | | | | |
|---|---|---|---|---|---|
| | 6–10 weeks | 10–14 weeks | 16–20 weeks | 22–26 weeks | 32–36 weeks |
| *Normal weight* | (*n* = 62) | (*n* = 65) | (*n* = 68) | (*n* = 71) | (*n* = 69) |
| TC | −0.5 (−3.1, 2.1) | −0.6 (−3.1, 1.8) | −0.9 (−2.9, 1.2) | −1.3 (−2.9, 0.3) | −1.2 (−3.1, 0.6) |
| LDL-C | −0.2 (−3.4, 3.1) | −0.9 (−4.0, 2.1) | −1.2 (−3.6, 1.3) | −1.5 (−3.4, 0.5) | −1.3 (−3.4, 0.8) |
| HDL-C | −4.1 (−10.4, 2.2) | −2.1 (−7.7, 3.6) | −1.0 (−6.4, 4.4) | −4.1 (−8.8, 0.6) | −3.6 (−8.6, 1.4) |
| TG | 1.1 (−0.4, 2.6) | 1.5 (0.1, 2.8)* | 0.7 (−0.8, 2.1) | 1.1 (0.0, 2.1)* | 0.9 (−0.1, 1.9) |
| *Obese/Overweight* | (*n* = 69) | (*n* = 71) | (*n* = 65) | (*n* = 71) | (*n* = 70) |
| TC | 0.3 (−3.5, 4.0) | 1.5 (−1.8, 4.7) | 0.1 (−3.3, 3.5) | 0.1 (−2.4, 2.5) | 0.4 (−2.3, 3.1) |
| LDL-C | 2.5 (−1.9, 7.0) | 2.8 (−1.1, 6.7) | 2.2 (−1.6, 6.1) | 0.9 (−2.1, 4.0) | 1.0 (−2.0, 4.1) |
| HDL-C | −7.7 (−16.1, 0.7) | −8.0 (−15.6, −0.4)* | −9.3 (−16.4, −2.1)* | −7.4 (−14.1, −0.7)* | −10.0 (−17.5, −2.3)* |
| TG | 0.4 (−2.3, 3.0) | 1.4 (−0.5, 3.2) | 0.7 (−1.2, 2.6) | 1.5 (0.1, 3.0)* | 1.9 (0.6, 3.2)** |

CI, confidence interval; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.
*$P \le 0.05$, **$P \le 0.01$.

**Table 3 Estimate of the effect size of maternal HDL-C measured between 32 and 36 weeks gestation on adjusted birth weight**

| HDL quartile | Mean HDL-C ± s.d. (mg/dl) | Difference in mean HDL-C[a] | Difference in adjusted birth weight (g)[b] |
|---|---|---|---|
| *Normal weight* | | | |
| 1 (lowest) | 60.3 ± 3.5 | Reference | Reference[c] |
| 2 | 70.4 ± 3.0 | 10.1 | −36.4 (−86.9, 14.1) |
| 3 | 80.5 ± 2.8 | 20.2 | −72.7 (−173.7, 28.3) |
| 4 | 100.3 ± 11.5 | 40.0 | −144 (-344, 56) |
| *Obese/Overweight* | | | |
| 1 (lowest) | 60.0 ± 4.1 | Reference | Reference[d] |
| 2 | 68.8 ± 1.9 | 8.8 | −88 (−154, −20.2) |
| 3 | 79.1 ± 4.3 | 19.1 | −191 (−334.3, −43.9) |
| 4 | 94.7 ± 8.2 | 34.7 | −347 (−607.3, −79.8) |

aBW, birth weight adjusted for gestational age at delivery; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.
[a]Calculated relative to the mean HDL-C concentration in the lowest quartile for each stratum (reference). [b]Calculated relative to the mean adjusted birth weight in the lowest HDL-C quartile for each stratum (reference). [c]A 1 mg/dl increase in HDL is associated with a −3.6 g (95% CI: −8.6, +1.4) change in aBW for normal weight women. [d]A 1 mg/dl increase in HDL is associated with a −10 g (95% CI: −17.5, −2.3) change in aBW for obese/overweight women.

in overweight/obese women, but is not statistically significant at any visit interval. Several cross-sectional studies have reported that maternal mid-pregnancy TG levels are positively associated with birth weight (12,13,25). The lack of a consistently significant TG effect in our sample may be a consequence of our modest sample size. Variation in aBW is not associated with variation in maternal serum TC or LDL-C for either stratum at any time point.

We performed multivariable longitudinal regression analyses of the influence of time-dependent variation in maternal serum HDL-C on variation in aBW (equation 1) for each BMI stratum. For overweight/obese women, the coefficient for $L_0$ in this model shows that a 13.0 g decrease in aBW (95% confidence interval: −22.6, −3.50) is significantly associated with a 1 mg/dl increase in the magnitude of maternal HDL-C measured at any time point during gestation; for normal weight women, a 6.4 g decrease in aBW (95% confidence interval: −13.5, 0.69) is associated with a 1 mg/dl increase in the magnitude of maternal HDL-C. In this model, there is no significant relationship between variation in aBW and variation in the rate of change in HDL-C in either the first ($L_{02}$) or second ($L_{24}$) half of pregnancy for either group. These results suggest that the magnitude of maternal HDL-C, not its trajectory, influences BW across pregnancy.

Finally, in Table 3, we illustrate the magnitude of the effect of maternal HDL-C measured between 32 and 36 weeks gestation on aBW. In this table, we use the regression coefficients in Table 2 to calculate the effect of the change in the mean maternal HDL-C across quartiles on the change in aBW. For overweight/obese women, there is a 347 g decrease in the mean aBW between the highest and lowest quartiles of maternal HDL-C. For normal weight women, there is only a 144 g decrease in mean aBW between these quartiles. This table clearly demonstrates that effects of HDL-C on BW are large and different between the strata.

## DISCUSSION

The regulation and effects of metabolic pathways may be substantially different in overweight and obese individuals compared to their normal weight counterparts (7–9,26). We have shown elsewhere that, overweight/obese women had significantly lower TC and LDL-C levels than normal weight women in late pregnancy. However, there were no differences in TG or HDL-C levels between the strata at any time point (10). Given these metabolic differences, this study is among the first to evaluate how the relationship between infant BW and maternal serum lipid levels may differ between these two groups.

The most striking finding from our study was a substantially larger inverse relationship between BW and HDL-C levels across pregnancy in overweight/obese women compared to their normal weight counterparts. Our results are consistent with smaller case–control studies that reported inverse associations between

maternal HDL-C levels and risk of macrosomia (5,12,14,15). While those studies controlled for maternal prepregnancy weight, they did not model the effects of metabolic factors in different BMI groups. Our results suggest that the effect of HDL-C on BW is very different in overweight/obese compared to normal weight women. In fact, the effect of HDL-C on BW was nearly twice as large at every time point in overweight/obese women (**Table 2**). These results suggest that the fetal growth response to maternal HDL-C, rather than the HDL-C levels themselves, was modified by maternal prepregnancy BMI.

The mechanisms through which maternal HDL-C may influence BW are poorly understood. However, HDL-C has several possible roles that could influence fetal growth and development (27). HDL has an important role in cholesterol homeostasis required to maintain a favorable sterol balance for the extra-embryonic fetal tissues to support fetal growth and development (28). For example, the placenta removes HDL from the maternal circulation at high rates (29). Perturbation of reverse cholesterol transport in overweight and obese women could affect the sterol balance in extra-embryonic fetal tissues (30). Although it does not cross the placenta, HDL may be able to affect fetal metabolism and growth *via* its effect on the metabolic function of extra-embryonic fetal tissues (28). For example, when maternal HDL-C concentrations decrease these tissues may have compensatory mechanisms for sterol uptake and processing that impact fetal growth (28). Maternal overweight and obesity may influence these compensatory mechanisms.

In addition to its role in cholesterol transport and homeostasis, HDL also has antioxidant, anti-inflammatory, and antithrombotic properties (27) that may influence placental circulation and fetal growth. For example, reduced levels of HDL-C may be associated with placental vasculopathy and risk of pre-eclampsia (31). It has been suggested that HDL-C–related factors associated with oxidative stress, such as paraoxonase, may influence vascular endothelial function and may be involved in the pathophysiology of these perinatal outcomes (31,32). The oxidative and inflammatory effects of HDL can be modified by a number of cytokines, hormones, and other factors (27). Thus, it is possible that dysregulation of adipocytokines in obese women (33) may modulate these effects of HDL-C during pregnancy. Ours appears to be the first study to suggest that effect of HDL-related pathways on fetal growth may be influenced by maternal obesity/overweight status.

A significant strength of our study is the prospective population-based cohort design. Few studies have systematically examined the relationship of lipid levels across pregnancy on infant outcomes such as BW. However, our study design inherently limits study participation to a group of women who present for early prenatal care and are able to attend multiple study visits. Women without prenatal care or with late, interrupted, or sporadic care are less likely to have been included. As a result, maternal sociodemographic covariates show limited variation. While our sample is homogeneous with regard to measures of socioeconomic status and race, there is considerable variation in prepregnancy BMI. Moreover, by focusing on this population, many potential confounding factors, both measured and unmeasured, are potentially accounted for by our sampling allowing us to focus on the effects of maternal overweight/obesity.

Our current sample size is modest. As a result, an extensive analysis of covariates, including maternal nutrition, illness, and behaviors that may influence the observed relationships was not possible. However, as noted above, controlling for sociodemographic variables that differed between the groups did not significantly change our results. A larger sample size will certainly allow for a more robust examination of physiologic biomarkers and epidemiological risk factors that influence the relationship of maternal obesity to infant BW. However, even with our limited sample size, our analyses consistently demonstrate that variation in maternal HDL-C levels measured across gestation influences infant BW differently in overweight/obese women compared to their normal weight counterparts.

Adiposity is associated with a complex set of metabolic and endocrinologic changes that may differ among subgroups of women with different BMIs (34). The effects of maternal adiposity on the growing fetus may be mediated by such changes (1,2). However, the physiological mechanisms underlying these effects are poorly understood. It has been speculated that metabolic factors in obese women may affect early placental functional development related to lipid and inflammatory responses (1). These early changes may alter the effects of both maternal lipid metabolism and placental transport of nutrients on the growing fetus. Our findings suggest that maternal-fetal HDL-C metabolism may have a significant role in these effects. We postulate that such differences may be involved in the "physiological programming" of the fetus that influences later risk of chronic disease. However, future studies to elucidate the details of such mechanisms will be needed. Alterations in maternal lipid metabolism may ultimately be a modifiable risk factor to prevent the consequences of maternal obesity on the offspring.

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## DISCLOSURE

The authors declared no conflict of interest.



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