Maternal Weight Gain Regulates Omega-3 Fatty Acids in Male, Not Female, Neonates: A Cross-Sectional Study

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Perrie F. O'Tierney-Ginn, PhD¹, Melanie Gillingham, RD, PhD²,
Jessica Fowler, MD³, Elizabeth Brass, MD⁴,
Nicole E. Marshall, MD^{5,6}, and Kent L. Thornburg, PhD^{6,7}

Abstract

The fetus largely depends on maternal supply and placental transport for its source of long-chain polyunsaturated fatty acids (LCPUFAs), which are essential for proper neurological and cardiovascular development. Pregnancy complications such as diabetes reduces neonatal LCPUFA supply, but little is known of how fatty acid delivery is affected by maternal body type or weight gain in uncomplicated pregnancies. In a cross-sectional study of maternal–neonatal pairs at term, we sought to determine the effect of gestational weight gain on neonatal LCPUFA supply. Forty maternal–neonatal pairs of uncomplicated (no gestational hypertension or diabetes) term pregnancies were recruited upon admission to Oregon Health & Science University Labor & Delivery for scheduled cesarean section. Maternal and umbilical cord plasma fatty acid profiles were measured using gas chromatography–mass spectrophotometry. First trimester weight gain was negatively correlated with maternal n-3 LCPUFA ($r = -0.80$, $P = .0002$), and this was not affected by fetal sex. High maternal weight gain in the first trimester was negatively associated with cord n-3 polyunsaturated fatty acid levels ($r = -0.70$, $P = .03$) and placental thickness ($r = -0.69$, $P = .03$) in male, but not female, offspring. High maternal weight gain in the first trimester is associated with a thinner placenta and low levels of n-3 LCPUFA in male offspring. Further study is required to confirm that male offspring are at a higher risk of poor outcomes associated with high maternal weight gain early in pregnancy.

Keywords

fatty acids, placenta, weight gain

Introduction

Maternal diseases like diabetes mellitus¹⁻³ and preeclampsia⁴ lead to reduced long-chain polyunsaturated fatty acid (LCPUFA) levels in umbilical cord blood. The fetus requires omega-3 (n-3) and omega-6 (n-6) LCPUFA for proper neurological and cardiovascular development. Deprivation of n-3 LCPUFA during pregnancy is associated with decreased visual acuity, behavioral abnormalities and cognitive impairment in infants,^{5,6} and hypertension in adult offspring.^{7,8} There is evidence that n-6 LCPUFA and their derivatives are proinflammatory, whereas n-3 LCPUFAs are anti-inflammatory.⁹⁻¹¹ Although the balance between n-6 and n-3 LCPUFA in utero is important for sustaining healthy tissues in early life, fetuses may often not receive adequate amounts of LCPUFA in either form even in uncomplicated pregnancies.^{12,13}

The fetus depends upon a rich maternal fatty acid reservoir and efficient placental transfer to meet its high demand for LCPUFA.¹⁴ Maternal LCPUFA levels reflect her diet, stores, and metabolism and may be affected by her prepregnancy body mass index (BMI).^{14,15} Although it would seem logical that

maternal levels of LCPUFA would be strongly influenced by physiological changes in early pregnancy including weight gain, the effects of gestational weight gain on maternal and fetal LCPUFA profiles are not known.

¹ Department of Reproductive Biology, Center for Reproductive Health, Case Western Reserve University, Cleveland, OH, USA

² Department of Molecular & Medical Genetics, Oregon Health and Science University (OHSU), Portland, OR, USA

³ Department of Obstetrics & Gynecology, UCLA, Los Angeles, CA, USA

⁴ Department of Obstetrics & Gynecology, Kaiser Permanente, Hillsboro, OR, USA

⁵ Department of Obstetrics & Gynecology, OHSU, Portland, OR, USA

⁶ Center for Developmental Health, OHSU, Portland, OR, USA

⁷ Department of Medicine (Cardiovascular Medicine), OHSU, Portland, OR, USA

Corresponding Author:

Perrie F. O'Tierney-Ginn, Department of Reproductive Biology, Center for Reproductive Health, Case Western Reserve University, 2500 MetroHealth Drive, R358, Cleveland, OH 44109, USA.

Email: poginn@metrohealth.org

Excessive maternal weight gain during pregnancy is known to be harmful to offspring as it is associated with high rates of macrosomia, emergency cesarean section, and obesity in the offspring later in life.¹⁶⁻¹⁹ Low weight gain during pregnancy places the developing fetus at risk of low birth weight, infection, seizures, cognitive deficits, and longer hospital stays.^{16,20} Although excess weight gain may be detrimental to a fetus,²¹ it is not known how maternal gestational weight gain affects fetal nutrient acquisition. While one might expect significant physiological differences in placental form and function between mothers on opposite ends of the weight gain spectrum, such speculation could only be based on very limited data. This is a large deficit in our understanding of the regulation of nutritional flow from mother to fetus. Based upon the known negative effects of excessive weight gain on offspring, we tested the hypothesis that high maternal gestational weight gain would be associated with depressed LCPUFA levels in maternal and cord plasma.

Participants and Methods

Participant Recruitment and Procedures

Forty women ≥ 18 years of age at term (≥ 37 weeks' gestation) were recruited based upon screening at admission to OHSU Labor & Delivery for scheduled cesarean section. Exclusion criteria included women carrying multiple fetuses, fetuses with chromosomal anomalies, fetuses with cardiac defects, gestational diabetes, preeclampsia, and maternal hypertension. Written, informed consent was obtained from each woman prior to cesarean section. Participant recruitment methods and tissue and data collection procedures were approved by the institutional review board of Oregon Health & Science University (OHSU; IRB#00005684).

Data and Tissue Collection

Maternal age, parity, smoking status, height, and weights throughout gestation were obtained from medical records. First-, second-, and third-trimester weight gains were calculated from recorded prepregnancy, early second-trimester (12-14 weeks), early third-trimester (26-28 weeks), and late third-trimester (38-39 weeks) weights. Total weight gain was calculated from the latest recorded third-trimester weight (38-39 weeks) and prepregnancy weight. Maternal venous blood was drawn immediately prior to cesarean section. Placental tissue and umbilical venous blood were collected at delivery. Placental weight (trimmed of cord and membranes), major and minor axial dimensions, and thickness were measured and recorded. Birth weight, crown-heel length, head circumference, gestational age at birth, and fetal sex were recorded. Umbilical blood was collected into EDTA-treated tubes and placed on ice until centrifuged at 1500g for 10 minutes at 4°C to isolate the plasma. Plasma was stored at -80°C.

Quantitative Plasma Fatty Acid Analysis

Fatty acids were extracted and quantified by a modification of the method of Lagerstedt et al²² as previously published.^{23,24} Deuterated free fatty acids ($d_3C14:0$, $d_3C16:0$, $d_3C18:0$, $d_3C20:0$, and $d_4C22:0$) were added to samples prior to extraction as internal standards. Following hydrolysis and extraction, fatty acids from 50 μ L of maternal and umbilical venous plasma were derivatized to the pentafluorobenzyl (PFB) esters. The fatty acid esters were analyzed by gas chromatography-mass spectrophotometry on a Trace DSQ (ThermoFinnigan) operating in the negative ion chemical ionization (NICI) mode with methane as the reagent gas. The fatty acid PFB esters were separated on a DB-5-MS capillary column (30 m $\times$ 0.25 mm $\times$ 0.25 μ m) with helium as the carrier gas at a flow rate of 1 mL/min. Individual fatty acids were monitored with selected ion monitoring and a dwell time of 50 milliseconds for each ion species. The NICI resulted in the loss of PFB and the formation of the stable carboxylate anion. Each fatty acid was matched to the deuterated internal standard closest in length and retention time. Peak area ratios of known amounts of standard fatty acids and the internal standards were used to generate calibration curves to quantify unknowns using Xcalibur software (Thermo Scientific, Waltham, MA).

Statistical Analysis

Two sample *t* statistics were used to examine differences in fatty acid concentrations between maternal and fetal plasma and between male and female umbilical plasma. We used Spearman correlation analysis to compare plasma fatty acid levels and lipids with maternal weight gain and prepregnancy BMI. Multiple regression analysis and stratification of males and females by maternal first-trimester weight gain was conducted to test for effects of fetal sex and first-trimester weight gain on placental dimensions and neonatal fatty acid profiles. Data are presented as mean (standard deviation, SD) unless noted otherwise. *P* value $< .05$ was considered statistically significant. All statistical calculations were carried out on STATA 10 statistical software (StataCorp LP, Texas).

Results

Table 1 displays maternal and placental characteristics in addition to birth weight, length, and head circumference data of male ($n = 18$) and female ($n = 22$) neonates. Neither prepregnancy BMI nor weight gain in the first or third trimesters was different between mothers of male or female offspring. Second-trimester weight gain was 35% higher in women carrying male fetuses compared to female fetuses ($P = .02$). Term placental weight was 25% greater in girls compared to boys, though birth weights were not different. Thus, male body weight gain per gram placenta exceeded that of female gain.

Table 1. Maternal, Placental, and Neonatal Characteristics.^a

	Males (n = 18)	Females (n = 22)
Maternal		
Age, years	32 (5)	30 (6)
Gestational age, weeks	39.1 (0.2)	39.1 (0.3)
Parity	2.2 (1.6)	2.1 (1.5)
Height, months	1.6 (0.1)	1.6 (0.1)
Currently smoking (Yes/No/unknown)	2/13/3	2/19/1
Prepregnancy BMI, kg/m ²	25.7 (6.7)	30.2 (7.2)
First-trimester weight gain, kg	5.0 (5.1)	2.9 (3.0)
Second-trimester weight gain, kg	6.3 (2.3)	4.1 (2.8) ^b
Third-trimester weight gain, kg	6.4 (5.5)	5.1 (3.2)
Total weight gain, kg	12.9 (4.3)	11.2 (5.4)
Placental		
Weight, g	469 (74)	584 (102) ^b
Width, cm	16.6 (2.5)	17.8 (1.8)
Length, cm	20.7 (3.6)	22.1 (3.3)
Thickness, cm	2.1 (0.4)	2.2 (0.3)
Neonatal		
Birth weight, kg	3.5 (0.6)	3.6 (0.4)
Crown-heel length, cm	50.6 (2.4)	51.2 (2.1)
Head circumference, cm	35.6 (1.9)	35.8 (1.3)
Birth weight: placental weight ratio, kg/kg	7.6 (1.1)	6.3 (0.8) ^b

Abbreviations: BMI, body mass index; SD, standard deviation.

^a Data are mean (SD).^b $P < .05$ by unpaired t test versus males.

Relationship Between Prepregnancy BMI and Weight Gain on Maternal and Neonatal Characteristics

Using weight data from the clinical records, we calculated recent prepregnancy BMI (mean (SD): 27.8 (7.1) kg/m²; $n = 20$), first-trimester weight gain (4.0 (4.3) kg; $n = 19$), second-trimester weight gain (5.2 (2.7) kg; $n = 35$), third-trimester weight gain (5.7 (4.4) kg; $n = 38$), and total weight gain (12.1 (4.8) kg; $n = 26$). We did not find associations between prepregnancy BMI with maternal age, parity, smoking, or gestational age at delivery. The same was true for weight gain. Prepregnancy BMI was positively associated with birth weight ($r = .45$, $P = .04$) but not birth length or head circumference. Maternal weight gain was not associated with neonatal weight, length, or head circumference at birth.

Maternal and Neonatal Plasma Fatty Acid Profiles

Maternal venous blood was obtained for 29 (73%) of the participants following an 8-hour presurgical fasting period. There were no detectable differences in maternal, placental, or neonatal characteristics between those from whom we did or did not obtain a maternal blood sample. Umbilical venous blood was obtained from all 40 participants.

Maternal and neonatal (umbilical vein) plasma fatty acid profiles are displayed in Table 2. Fatty acids were analyzed using individual plasma concentrations ($\mu\text{mol/L}$) and also as a proportion of total fatty acid levels (% total). Plasma concentrations of all individual fatty acids were higher in maternal plasma than in cord blood. However, relative to all other fatty

Table 2. Maternal and Neonatal Plasma Fatty Acid Profiles.^a

	Maternal	Umbilical Vein	
		Male	Female
$\mu\text{mol/L}$	n = 29	(n = 18)	(n = 22)
Myristic acid, 14:0	972 (405)	131 (37) ^b	135 (27) ^b
Palmitic acid, 16:0	4996 (1643)	1244 (259) ^b	1392 (232) ^b
Stearic acid, 18:0	889 (204)	328 (75) ^b	387 (75) ^b
Total SFA	6858 (2072)	1703 (355) ^b	1914 (315) ^{b,c}
Myristoleic acid, 14:1	14.6 (7.6)	3.7 (1.1) ^b	3.6 (0.9) ^b
Palmitoleic acid, 16:1	492 (231)	132 (42) ^b	144 (37) ^b
Oleic acid, 18:1	2160 (1086)	309 (181) ^b	319 (139) ^b
Total MUFA	2667 (1164)	444 (217) ^b	466 (168) ^b
Linoleic acid, 18:2	2536 (712)	188 (175) ^b	200 (123) ^b
Arachidonic acid, 20:4	1236 (471)	721 (412) ^b	659 (288) ^b
Total n-6	3773 (1026)	909 (565) ^b	859 (401) ^b
α -Linolenic acid, 18:3	64.7 (17.9)	6.1 (4.0) ^b	6.7 (2.9) ^b
Eicosapentaenoic acid, 20:5	76.3 (81.7)	27 (18) ^b	20 (6) ^b
Docosahexaenoic acid, 22:6	356 (248)	167 (111) ^b	118 (67) ^b
Total n-3	497 (334)	199 (125) ^b	144 (74) ^b
Total PUFA	4269 (1296)	1109 (668) ^b	1002 (462) ^b
n-6/n-3	9.3 (3.4)	5.0 (1.6) ^b	6.3 (1.9) ^{b,c}
Total FA	13794 (4245)	3256 (1101) ^b	3381 (807) ^b
%SFA	50 (4)	54 (10) ^b	58 (8) ^b
%MUFA	19 (2)	13 (4) ^b	14 (3) ^b
%n-6	28 (4)	27 (7)	24 (6)
%n-3	3.5 (1.5)	6.0 (2.9) ^b	4.1 (1.4) ^{b,c}
%PUFA	31 (5)	33 (8)	29 (7)

Abbreviations: FA, fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SD, standard deviation; SFA, saturated fatty acid.

^a Values are mean (SD).^b $P < .05$ by paired t test versus corresponding maternal plasma fatty acid.^c $P < .05$ by unpaired t test versus corresponding male UV plasma fatty acid.

acids, neonates had a higher percentage of n-3 LCPUFA than their mothers. Percentage of total fatty acids that were saturated was also higher, while percentage of monounsaturated was lower in neonates as compared to their mothers.

Male and female neonates had some notable differences in umbilical plasma fatty acid profiles. The n-6/n-3 LCPUFA ratio was 26% higher in female neonates and they had a lower proportion of n-3 LCPUFA relative to total fatty acids than males. We also observed a higher saturated fatty acid concentration in female neonates. These sex differences were no longer statistically significant when maternal first-trimester weight gain was accounted for (using multiple regression or stratification by weight gain). Total fatty acid concentrations did not differ between sexes.

Maternal Fatty Acid Profiles at Term Are Associated With First-Trimester Weight Gain

Maternal first-trimester weight gain data were available for 19 participants (10 with male fetuses and 9 with female fetuses). Maternal weight gain in the first trimester was related to fatty acid profiles in maternal plasma at term, but maternal fatty acid

Figure 1. Maternal plasma long-chain polyunsaturated fatty acids were associated with first-trimester weight gain. Maternal total n-3 long-chain polyunsaturated fatty acid (LCPUFA; A) concentrations were negatively associated with her weight gain in the first trimester of pregnancy. The n-6/n-3 LCPUFA ratio was positively associated with first-trimester weight gain (B). $P < .05$ by pairwise Spearman correlation ($N = 16$).

levels were not associated with prepregnancy BMI, second-, or third-trimester weight gain. Maternal plasma arachidonic acid ($r = -.50$, $P = .049$), eicosapentaenoic acid ($r = -.70$, $P = .003$), docosahexaenoic acid (DHA) ($r = -.79$, $P = .0003$), total n-3 LCPUFA ($r = -.80$, $P = .0002$; Figure 1A), and total polyunsaturated fatty acid ($r = -.68$, $P = .004$) were all negatively associated with first-trimester weight gain. The maternal n-6/n-3 ratio ($r = .75$, $P = .0009$; Figure 1B) and the proportion of maternal saturated fat ($r = .56$, $P = .02$) were positively associated with first-trimester weight gain, whereas the proportion of n-3 LCPUFA ($r = -.80$, $P = .0002$) was inversely related to early pregnancy weight gain.

Fatty Acid Profiles in Male Neonates Are Associated With First-Trimester Weight Gain in Mothers

In male neonates, umbilical venous plasma DHA ($r = -.66$, $P = .04$), total n-3 LCPUFA ($r = -.70$, $P = .03$; Figure 2A),

and the proportion of n-3 LCPUFA ($r = -.70$, $P = .03$) were negatively associated with first-trimester weight gain, whereas the n-6/n-3 ratio ($r = .66$, $P = .04$; Figure 2B) was positively associated. In females, only plasma myristic acid was associated with first-trimester weight gain ($14:0$, $r = .78$, $P = .02$). Total fatty acid levels in neonates did not correlate with first-trimester weight gain in either sex. Neonatal fatty acid profiles in neither sex were associated with second- or third-trimester weight gains. Neonatal fatty acid levels were not associated with prepregnancy BMI.

Correlation Between Maternal and Neonatal Fatty Acid Profiles Is Sex Specific

Umbilical venous fatty acid levels were positively correlated with maternal levels only in male neonates. Neonatal total n-3 LCPUFA concentrations ($r = .64$, $P = .005$) and the n-6/n-3 ratio ($r = .70$, $P = .002$), along with the relative proportion of saturated ($r = .55$, $P = .02$), polyunsaturated ($r = .56$, $P = .02$), and n-3 LCPUFA ($r = .76$, $P = .0004$) fatty acids were correlated with the respective maternal fatty acids in males. Maternal and female cord fatty acids did not correlate.

Placental Dimensions

Placental thickness was negatively associated with first-trimester weight gain in male but not in female fetuses ($r = -.69$, $P = .03$; Figure 3). Other placental measurements (weight, width, and length) were not associated with maternal weight gain. As expected, placental weight from male and female fetuses combined was positively associated with prepregnancy BMI ($r = .58$, $P = .007$).

The proportion of n-3 LCPUFA ($r = .51$, $P = .04$) and the n-6/n-3 ratio ($r = -.54$, $P = .02$) was positively and negatively associated with placental thickness, respectively. The total monounsaturate ($r = -.44$, $P = .04$) levels and the proportion of monounsaturates ($r = -.62$, $P = .002$) in plasma of female neonates were negatively associated with placental thickness. No other associations were detected between placental weight or other dimensions and neonatal lipids in males or females.

Discussion

The primary finding of this study is that maternal weight gain in the first trimester, but not in later trimesters, was strongly associated with maternal and neonatal plasma fatty acid profiles at term. Another finding was that maternal first-trimester weight gain correlated with neonatal fatty acid levels in males but not in females. These data suggest that the physiological adaptation by the mother in the first 3 months of pregnancy determines placental growth and the subsequent lipid profile in offspring in a sex-dependent manner.

Maternal fatty acid profiles change during early pregnancy but little thereafter²⁵ raising important questions: what is the biological link between maternal weight gain in the first trimester and the levels of n-3 LCPUFA in the maternal plasma at

Figure 2. Plasma long-chain polyunsaturated fatty acids were associated with first-trimester weight gain in male neonates. Total n-3 long-chain polyunsaturated fatty acid (LCPUFA; A) levels were negatively associated with first-trimester weight gain in male fetuses. The n-6/n-3 LCPUFA ratio was positively associated with first-trimester weight gain in males (B). No association between weight gain and plasma LCPUFA was detected in female offspring. $P < .05$ by pairwise Spearman correlation ($n = 10$ males, $n = 9$ females).

term? Are the lipid profile regulation systems in the maternal liver plastic only during that period of time? These questions reveal important gaps in knowledge in the field.

It is known that weight loss in obese individuals following bariatric surgery is associated with increases in their plasma levels of the LCPUFA AA and DHA.^{26,27} Thus, an increase in maternal fat mass in the first trimester may be a driving force for the observed opposite effect: decreases in maternal plasma n-3 LCPUFA. Maternal dietary composition may be an additional factor. Women eating nutrient poor diets are more likely to gain weight in the low or high extremes during pregnancy.²⁸ Furthermore, nonhuman primates fed a high-saturated fat diet have lower plasma n-3 LCPUFA during pregnancy as do their offspring.²⁹ Thus, specific fatty acid profiles in maternal blood may be related to specific diets even independent of first-trimester weight gain. In addition, there may be other physiological drivers of weight gain that are associated with maternal blood lipid regulation.

One of the most striking findings in the present study is that levels of plasma n-3 LCPUFA found in male cord blood closely mirror levels found in their mothers—decreasing with increasing gestational weight gain. The disassociation between maternal fatty acids and that of her female offspring may signify a placental or fetal adaptation protecting female offspring from variations in maternal fatty acid availability. This is consistent with the idea of a conservative female growth strategy,³⁰ whereby females are less influenced than male fetuses by variations in maternal diet,^{31,32} weight gain, and body composition.³³ Conversely, the male-specific growth strategy is characterized by a highly efficient placenta that, in teleological terms, sacrifices placental mass and its safety net in order for the fetus to grow as rapidly as possible.³⁰ Consistent with this, we found that placental thickness is reduced in proportion to maternal weight gain in the first trimester of pregnancy in male offspring. Placentas alter their growth according to their nutritional environment, particularly early in pregnancy.^{34,35}

Figure 3. Placental thickness is associated with first-trimester weight gain. High first-trimester weight gain is associated with a thin placenta in male but not female neonates at birth. $P < .05$ by pairwise Spearman correlation ($n = 10$ males, $n = 9$ females).

A reduction in placental growth in response to high-energy intake early in pregnancy has been shown previously in sheep³⁶ and humans.³⁷

In the latter half of pregnancy when fetal requirements for LCPUFA are at their highest, maternal n-3 LCPUFA levels are depressed in women with high first-trimester weight gain. Our data suggest that LCPUFA supply is maintained in females with relatively large and thick placentas; but in males who have smaller and thinner placentas, LCPUFA transport is apparently insufficient resulting in reduced cord n-3 LCPUFA levels at birth. Placental disc thickness is a crude measure of villous arborization and thus nutrient exchange surface area.³⁸ We speculate that placental thickness mediates neonatal LCPUFA supply to males. Thus, male fetuses of women with high first-trimester weight gain have a low n-3 LCPUFA concentration in cord blood and a high n-6/n-3 ratio. This fatty acid profile may place them at risk for cardiovascular disease and obesity later in life.^{7,39}

Males have higher nutritional requirements in general as evidenced by studies showing that women carrying male fetuses take in more nutrients (particularly lipids) and usually have higher weight gain than those carrying females.⁴⁰ Consistent with this, we report that women carrying males gained more weight in the second trimester than those carrying females. First-trimester weight gain accounted for sex differences in plasma fatty acid profiles in the neonates. Thus, maternal weight gain may impact supply of fatty acids to the growing fetus.

The relatively small number of participants in this study allowed us to perform in-depth fatty acid profiling in our Participants, though limits the generalizability of our conclusions. Due to difficulties securing clinic-recorded prepregnancy weights, our first-trimester and prepregnancy BMI data were limited to ~20 women. However, similar to larger cohorts,⁴¹⁻⁴³ we found strong relationships between prepregnancy BMI and

placental and birth weights. The robust relationships presented here between first-trimester weight gain and fatty acids were subjected to conservative statistical analysis but would benefit further from a much larger study.

In 2009, the Institute of Medicine (IOM) released new guidelines recommending that women gain only 1 to 3 kg in the first trimester.²¹ The range of weight gain for women in our study was 1 to 10 kg, with 1 participant gaining more than 15 kg in the first trimester. We found that women with high first-trimester weight gain had low levels of n-3 LCPUFA in their plasma, irrespective of fetal sex. However, only the male offspring of these women had correspondingly low n-3 LCPUFA levels, which may be due to placental thinness in these neonates.

We conclude that weight gain in the first trimester is critically important to maternal and male neonatal LCPUFA levels at term. Our findings support the recommendations of the IOM and caution against excessive weight gain in the first trimester.

Authors' Note

This work was performed at Oregon Health and Science University. PFOG and KLT designed the study and drafted the manuscript. PFOG, JF, EB, and NM participated in recruitment of study participants and collection of materials. PFOG performed all assays. PFOG, MG, and KLT analyzed the data. All authors made critical revisions and approved the manuscript.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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