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Association of Elevated, Free Fatty Acids During Late Pregnancy With Preterm Delivery

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Abstract

Objective—To examine the association between moderately elevated maternal plasma free fatty acids (FFAs) during late pregnancy and preterm delivery.

Methods—In a prospective observational cohort with 523 healthy pregnant women, fasting plasma FFAs were measured during the 3rd trimester; socioeconomic, demographic, and anthropometric parameters were collected at entry to prenatal care; pregnancy outcomes were abstracted from medical record at delivery.

Results—After control for confounders including pre-pregnant body mass index (multiple logistic regression analysis), women who had moderately elevated plasma FFAs (in the highest tertile), showed a greater than 3-fold increased risk of preterm delivery (adjusted odds ratio (AOR) 3.49, 95% confidence interval (CI) 1.73, 7.03, p<0.001). The associations persisted in women who had spontaneous preterm delivery (AOR 2.35, 95% CI 1.05, 5.28, p<0.05) and after excluding women with gestational diabetes mellitus and preeclampsia (AOR 3.30, 95% CI 1.38, 7.87, p<0.01). Additional stratified analyses showed that the association of high maternal FFAs and increased risk of preterm delivery was independent of pre-pregnant obesity.

Conclusion—Elevated fasting plasma FFA levels at 30 weeks' gestation were associated with an increased risk of preterm delivery. This effect was independent of pre-pregnant obesity and several other known risk factors for preterm delivery including cigarette smoking, ethnicity and prior preterm delivery. These data may have important clinical significance because they provide a possible link between preterm delivery and high lipid levels, a known risk factor for cardiovascular disease.

Introduction

Preterm delivery is defined as birth occurring prior to 37 completed weeks' gestation.[1] It complicates 12–13% of all births in the United States.[2] The rate of preterm delivery increased 30% between 1981 and 2004 and is highest in African Americans.[2–3] Preterm delivery is not only a leading cause of neonatal morbidity and mortality;[1–2] its long-term sequelae pose a serious problem for the offspring and for the mother.[4–7] There is increased insulin resistance in children born preterm which may be a risk factor for the development of type 2 diabetes mellitus.[4] More recently, the delivery of a preterm infant has been linked to increased cardiovascular morbidity and mortality for the mother later in life.[5–7] However it is important to recognize that data from retrospective studies are subject to confounding by and bias from

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imprecise maternal recall and/or coexisting complications of pregnancy such as preeclampsia or diabetes. [6–7]

Mechanisms that link preterm delivery with excess maternal cardiovascular disease (CVD) risk are not understood. It is unclear whether underlying risk factors for CVD, such as elevated circulating levels of triglycerides or cholesterol, are a marker for increased risk of preterm delivery in pregnant women.[5–6] It is known that plasma triglyceride levels increase during late pregnancy and that enhanced lipolytic activity plays a key role in making free fatty acids (FFAs) available to the fetus.[8] However, the influence of elevated maternal FFAs on risk of preterm delivery has not been extensively examined in epidemiological studies. We therefore investigated the relationship of elevated maternal plasma FFAs on risk of preterm delivery and other related outcomes in a cohort of 523 healthy young pregnant women from Camden, NJ.

Materials and Methods

The study was conducted in the Osborn Family Health Center, Our Lady of Lourdes Medical Center in Camden, NJ. Data were collected as part of the Camden Study, a prospective cohort study of pregnancy outcome and complications in young, generally healthy women residing in one of the poorest cities in the continental United States.[9] the institutional review board at the University of Medicine and Dentistry of New Jersey - SOM approved the study protocol. Informed written consent was obtained at enrollment (on average at week 16.23 ± 0.32, mean ± SE) from each participant after explanation of the nature and purpose of the study.

Study participants were enrolled between July 2000 and July 2004. Twenty-four (3.5%) women screened for eligibility were excluded from participation because of serious non-obstetric problem (e.g. Lupus, type 1 or 2 diabetes, seizure disorders, malignancies, acute or chronic liver disease, drug or alcohol abuse and psychiatric problems). Women with gestation greater than 28 week were also excluded from participation. Eighty percent of the patients who were eligible agreed to participate in this study. A final total of 523 pregnant women were included in this analysis.

Data and blood samples collection and analytic procedures

Data of socioeconomic, demographic and lifestyle were obtained by interview at entry to care and updated by week 28 gestation. Ethnicity was self-defined. BMI was computed based on self reported pregravid weight and measured height at entry to prenatal care (kg/m^2). Maternal obesity was defined as BMI > 29.[10] Fasting blood samples (>8 hours) were obtained to measure plasma FFA concentrations during the 3rd trimester (obtained at 30.96 ± 0.16 weeks of gestation, mean ±SE). Samples of non-heparinized plasma were centrifuged at 4°C and stored at −70°C for assay. FFA levels were determined spectrophotometrically by an enzymatic assay kit (Wako Chemicals USA, Inc. Richmond, VA). The coefficient of variation within and between assays was <5%.

Preterm delivery and other related pregnancy outcomes

Pregnancy outcome and complications were obtained by abstracting the prenatal, labor, delivery and newborn medical record. Gestational duration was based upon gestation from participants' last normal menstrual period confirmed or modified by ultrasound. Preterm delivery (delivery before 37 completed weeks), infant admission to the neonatal intensive care unit (NICU) and low birth weight (LBW, <2500 g) were used as confirmatory outcome variables in the analysis. Gestational diabetes mellitus (GDM) was diagnosed using the criteria from Carpenter/Coustan conversion as recommended by the American Diabetes Association.[11] Preeclampsia was diagnosed as described previously in the literature.[12] Small-for-

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gestational age (SGA) was defined as a neonatal birth weight is lower than the 10th percentile for gestational age and adjusted for ethnicity, parity and infant gender by Zhang's standard.[13]

Statistical analysis

Means were computed and one-way analysis of variance (ANOVA) was used to assess the association between maternal background characteristics and FFAs; the Chi-square test was used to assess differences in categorical variables. Analysis of variance was used to compare mean FFAs levels after adjustment for potential confounding variables. ANOVA and chi-square with planned contrasts were used to assess the significance of the linear trend when the independent variable of interest was a categorized continuous variable or a categorical variable. Because of a skewed distribution, FFAs were coded into tertiles and the highest tertile (>432 μmol/l, high FFAs) was compared to other tertiles pooled (≤432 μmol/l). Logistic regression was used when the dependent variable (preterm birth, NICU, LBW) was dichotomous. Logistic regression coefficients and their standard errors were used to compute odds ratios (OR), adjusted odds ratios (AOR) and 95% confidence intervals (CI). Potential confounding variables known associated with preterm delivery including maternal age, pre-pregnant BMI, ethnicity, parity, cigarette smoking, and prior preterm delivery were included in multivariable models. An analysis that stratified by maternal obesity and FFA level was performed as well. All statistical analyses were performed using SAS v.9.1 (SAS Institute, Inc., Cary, NC).

Results

When maternal characteristics were examined according to plasma FFA tertile (table 1), we found positive linear relationships between plasma FFAs and maternal age (p for trend <0.001), nulliparity (p for trend <0.05) and pre-pregnant BMI (p for trend <0.001). A weak but significant negative relationship between FFAs and gestational age at delivery was also observed (p for trend <0.05). Other variables including ethnicity, cigarette smoking, timing of the preterm delivery (≤34 vs >34 weeks) and gestation at blood sample collection were not significantly related to FFA tertile.

Plasma FFA levels were higher in women with preterm delivery (n=39) compared to women who delivered term (mean ± SE, 430.5 ± 24 vs 379.7 ± 6.9 μmol/l, p<0.05) after control for maternal age, pre-pregnant BMI and ethnicity. Women in the highest tertile of plasma FFA had a 3.4-fold greater risk of preterm delivery (table 2, model 1, AOR 3.43, 95% CI 1.70, 6.88, p<0.001) after control for confounders including prior preterm delivery. This effect persisted after an additional adjustment for pre-pregnant BMI (model 2, AOR 3.49, 95% CI 1.73, 7.03, p<0.001).

The associations between high FFAs and preterm delivery remained significant after women with medically indicated preterm delivery (n=11, including preeclampsia (N=8), gestational diabetes (N=1), other (N=2)) were excluded (table 2, model 1, AOR 2.29, 95% CI 1.03, 5.13 and model 2, AOR 2.35, 95% CI 1.05, 5.28) as well as after excluding 24 women who developed GDM (N=1 preterm delivery) or 42 with preeclampsia (N=13 preterm deliveries; a total of 4 with both GDM and preeclampsia) (AOR 3.18, 95% CI 1.34, 7.55 and AOR 3.30, 95% CI 1.38, 7.87, model 1 and model 2 respectively, p < 0.01 for both, table 2). Thus, an elevation in FFA level was associated with an increased risk of preterm delivery.

Because FFA concentrations were positively correlated with pre-pregnant BMI (table 1) and maternal obesity is a known risk factor or confounder for adverse pregnancy outcomes, we examined whether maternal obesity was associated with preterm delivery. Our data suggested that maternal obesity (pre-pregnant BMI >29) was not associated with preterm delivery (6.9% vs 7.67%, obese vs non-obese, chi-square 0.09, p=0.76). Four new variables were created to further explore the combined effect of FFAs and maternal obesity on risk of preterm delivery.

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Using non-obese women (pre-pregnant BMI ≤ 29) with low FFAs (≤432 μmol/l) as the reference, we found that women with high FFAs, regardless of whether they were obese (AOR 2.85, 95% CI 1.06, 7.71, p<0.05) or not obese (AOR 3.33, 95% CI 1.48, 7.47, p<0.01) had similar risks of delivering a preterm infant, whereas obese women with low FFAs were not at risk (AOR 0.53, 95% CI 0.12, 2.45, table 3).

We also tested whether high FFAs were also associated with increased risks of NICU admission and infant LBW since 58% of infant admissions to the NICU and 62% of infants with LBW from the cohort were delivered preterm. High maternal FFAs were associated with nearly 2-fold increased risk of infant admission to the NICU (table 4, AOR 1.95, 95% CI 1.09, 3.49, p<0.05) and a 2-fold increased risk of LBW infant (AOR 2.10, 95% CI 1.00, 4.42, p <0.05) after adjustment. High FFAs were not associated with the delivery of SGA infants (6.92% vs 6.82%, low FFAs vs high FFAs, chi-square 0.002, p=0.97).

Discussion

We have demonstrated that moderately elevated maternal plasma FFAs, measured early in the third trimester, were associated with an increased risk of preterm delivery. Our data analysis was performed with adjustment for known potential confounders that also influence risk of preterm delivery.

We found that plasma FFAs in the highest tertile were associated with a 3-fold increased risk of preterm delivery after a multivariable adjustment including pre-pregnant BMI (table 2). This relationship persisted in women who had spontaneous preterm delivery. Since pregnancy complicated by GDM or preeclampsia is associated with dyslipidemia and has an increased risk of preterm delivery,[14–16] separate analysis with exclusion of all women diagnosed with GDM or preeclampsia (including both term and preterm delivery) was performed. We found that high FFAs also were associated with more than 3-fold increased risk of preterm delivery in women without GDM or preeclampsia (table 2).

Preterm delivery is known to be initiated by multiple mechanisms.[1,17] Data on hyperlipidemia in women who deliver preterm is limited. Catov et al reported that an elevation in maternal non-fasting plasma triglyceride or cholesterol level early in gestation was associated with a greater than 2-fold increased risk of preterm delivery, thus suggesting the presence of dyslipidemia in women with spontaneous preterm delivery.[5] However, maternal triglycerides do not directly cross the placenta.[8,18–19]

We have several hypotheses for why high FFAs may increase risk of spontaneous preterm delivery. First, maternal circulating FFAs can be transferred to the fetus across the placenta. In support of this hypothesis was the observation that maternal plasma total FFAs were positively correlated with cord plasma FFAs.[18] These include the essential (dietary) FFAs and their metabolically important derivatives such as arachidonic acid, a precursor of the eicosanoids including prostacyclins and prostaglandins.[17,20] It is known that prostaglandins, play an important role by stimulating the uterine contractions that drive preterm delivery.[1, 17] Reece et al reported a higher proportion of maternal RBC and plasma arachidonic acid in preterm cases compared with controls.[19] Thus, this could be indirect evidence for excessive maternal arachidonic acid availability or mobilization in preterm labor.[19] In the current study, we did not have evidence about whether or not arachidonic acid was increased in women with high FFAs.

Second, high FFAs may link to proinflammatory pathways. Preterm labor is recognized as an inflammatory phenomenon, even in the absence of infection.[20–22] Specific unsaturated fatty acids, particularly the essential fatty acid linoleic acid, which comes from the maternal diet, selectively stimulate the development of a proinflammatory response in human endothelial

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cells studied in vitro.[22] Increases in inflammatory cytokine formation in human decidua stimulate prostaglandins synthesis.[20] Thus, high maternal circulating FFAs could be linked to inflammation, a known risk factor for preterm delivery.

The causes of and risk factors for preterm delivery are not completely understood. Plasma FFA concentrations are commonly elevated during late pregnancy and high levels may serve as marker of maternal risk for conditions other than preterm delivery. During pregnancy, higher FFAs are linked to increased insulin resistance and hypertensive disorders of pregnancy as well as to impaired glucose metabolism.[23–24] However, as with many other biomarkers, the practical usefulness in the case of an individual women and the cutpoint for dyslipidemia during pregnancy, including the definition of high FFAs, has not been established for preterm birth and needs to be confirmed in the future studies.

Pre-pregnant obesity is associated with a variety of adverse pregnancy outcomes[25–26] but it relation to preterm delivery is conflicting.[15,27] Because the concentration of maternal plasma FFAs was positively correlated with pre-pregnant BMI (table 1), we adjusted pre-pregnant BMI in all analyses (table 2 and 4). In addition, with a relatively large sample size, we were able to perform stratified analysis on BMI, FFAs and preterm delivery (table 3). There were 67 (12.8%) women who were obese and had high FFA levels. It was confirmed that high FFAs (in women who were either obese or not obese) were associated with a 2 to 3-fold increased risk of preterm delivery, after a multivariable adjustment (table 3). Pre-pregnant obesity per se did not impact preterm risk (6.90 vs 7.67%, p=0.76).

Additionally, FFAs in the highest tertile are also associated with increased risk of infant admission to NICU and risk of LBW, two conditions related to preterm delivery. We observed that a high FFAs level was associated with a nearly 2-fold increased risk to infant admission to NICU or low birth weight (<2500 g) (table 4). We did not observe the same relationship between high FFAs and SGA infant. Since 62% of low birth weight infants and 58% of infant admitted to the NICU were delivered preterm, these results support the relation between high FFAs and increased risk of preterm delivery.

There are several limitations to this study. Firstly, twenty percent eligible patients did not agree to participate the study. Their demographic, socioeconomic, or medical characteristics could bias outcome measures in some way although we believe any effect should be small. Secondly, FFAs concentration was measured at 30 weeks gestation, which was 2–6 weeks prior to the preterm delivery. FFAs level early in gestation could potentially provide additional information on risk earlier in gestation. Thirdly, our results from the specific ethnic groups may not be generalizable to other populations. Socioeconomic factors such as dietary intake may affect FFAs concentration as well as increasing risk. Finally, while we had adequate statistical power to detect risk of preterm delivery when comparing the highest FFA tertile to the other two tertiles pooled (power=88%, 2 sided test with α=5%), power of some sub-analyses was lower (44–66%, 2 sided test and 55–74%, 1 sided test).

In conclusion, the current study demonstrated that at the 3rd trimester, plasma FFAs in the highest tertile were associated with a greater than 2-fold risk of preterm delivery. This effect was independent of pre-pregnant obesity and several other known risk factors for preterm delivery including cigarette smoking, ethnicity and prior preterm delivery. Elevated maternal FFA levels may play a role in the mechanisms underlying preterm delivery or may simply be a marker of risk. These data have potential clinical significance in that they provide a link between dyslipidemia, a well-known risk factor for CVD, and preterm delivery.

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Table 1

Plasma free fatty acid concentrations (by tertile) and characteristics of study subjects

	All subjects (n=523)	Tertile 1 (n=173)	Tertile 2 (n=174)	Tertile 3 (n=176)	P for trend*
FFA (µmol/l)		<299	299–432	>432	
FFA median (µmol/l)	364	231	364	531	
Age (yr)	22.70 ± 0.23	21.68 ± 0.39†	22.76 ± 0.39‡	23.70 ± 0.39	< 0.001
Pre-pregnant BMI (kg/m^2)	26.06 ± 0.28	24.88 ± 0.48†	25.97 ± 0.48	27.30 ± 0.48	< 0.001
Cigarette smoking (%)	90 (17.20)	33 (19.08)	32 (18.39)	25 (14.20)	0.426
Nulliparas (%)	198 (37.86)	79 (45.66)	65 (37.36)	54 (30.68)	
Parous	325 (62.14)	94 (54.34)	109 (62.64)	122 (69.32)	< 0.05
Ethnicity (%)					
Hispanic	279 (53.35)	87 (50.29)	102 (58.62)	90 (51.14)	
African-American	181 (34.61)	60 (34.68)	53 (30.46)	68 (38.64)	
Caucasian and other	63 (12.05)	26 (15.03)	19 (10.92)	18 (10.23)	0.287
Medicaid (%)	517 (99.04)	172 (99.42)	171 (98.84)	174 (98.86)	0.821
Gestational age at blood collection (wks)	30.96 ± 0.16	30.91 ± 0.27	31.13 ± 0.27	30.84 ± 0.27	0.940
Gestational age at delivery (wks)	38.79 ± 0.07	38.87 ± 0.13§	38.98 ± 0.13‖	38.52 ± 0.13	< 0.05
Preterm delivery					
≤ 34 wks gestation	13 (33.33)	3 (27.27)	1 (20.00)	9 (39.13)	
34.1 - < 37 wks gestation	26 (66.67)	8 (72.73)	4 (80.00)	14 (60.87)	0.628

Data are mean ± SE for continuous variables computed by ANOVA and n (%) for categorical variables by Chi-square.

* P for trend by ANOVA or P value from Chi-square test

† p<0.001 vs tertile 3

‡ p<0.05 vs tertile 1

§ p<0.01 vs tertile 3

‖ p<0.05 vs tertile 3

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Table 2

Elevated plasma FFA concentrations and risk of preterm delivery

FFA(μmol/l)	Total N	Preterm/ Term (N)	Unadjusted % Preterm	OR (95% CI)	Model 1†	AOR (95% CI) Model 2‡
Preterm delivery						
Tertiles 1&2	347	16 / 331	4.61	1.00	1.00	1.00
Tertile 3	176	23 / 153	13.07	3.11 (1.60,6.06)	3.43 (1.70, 6.88)§	3.49 (1.73,7.03)§
Spontaneous preterm delivery*						
Tertiles 1&2	345	14 / 331	4.06	1.00	1.00	1.00
Tertile 3	167	14 / 153	8.38	2.16 (1.01, 4.65)	2.29 (1.03, 5.13)//	2.35 (1.05, 5.28)//
Preterm delivery without GDM or preeclampsia*						
Tertiles 1&2	312	11 / 301	3.53	1.00	1.00	1.00
Tertile 3	149	14 / 135	9.40	2.84 (1.26, 6.41)	3.18 (1.34, 7.55)¶	3.30 (1.38, 7.87)¶

*Spontaneous preterm delivery, women with medically indicated preterm delivery (n=11) were excluded; Women with gestational diabetes mellitus (GDM, n=24) and preeclampsia (n=42) were excluded. Four women had both GDM and preeclampsia.

†Model 1 was adjusted for age, ethnicity, parity, cigarette smoking and prior preterm delivery for outcome variables of preterm delivery and spontaneous preterm delivery.

‡Model 2 was adjusted for all variables in Model 1 and additionally for the variable of pre-pregnant BMI.

§p<0.001

//p<0.05

¶p<0.01

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Table 3

Elevated plasma FFA concentrations, maternal obesity and risk of preterm delivery

Combined FFA & obese[†]	N	Unadjusted % Preterm	OR (95% CI)	AOR (95% CI)[*]
Non-obese and low FFA	269	5.20	1.00	1.00
Non-obese and high FFA	109	13.76	2.91 (1.35,6.25)[‡]	3.33 (1.48, 7.47)[‡]
Obese and low FFA	78	2.56	0.48 (0.11, 2.16)	0.53 (0.12, 2.45)
Obese and high FFA	67	11.94	2.47 (0.99, 6.16)	2.85 (1.06, 7.71)[§]

[†] Obese is defined as pre-pregnant BMI >29; low FFA is FFA concentration ≤432 μmol/l; high FFA is FFA concentration >432 μmol/l. Non-obese and low FFA was used as referent group.

[*] Model was adjusted for age, ethnicity, parity, cigarette smoking and prior preterm delivery.

[‡] $p<0.01$

[§] $p<0.05$

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Table 4

Association of high plasma FFA concentrations with low birth weight (LBW) and neonatal intensive care unit admission (NICU)

FFA (μmol/l)	N	NICU/ Non-LBW (N)	Unadjusted % NICU / LBW	OR (95% CI)	AOR (95% CI)*
Infant in NICU					
Tertiles 1&2	347	29 / 318	8.38	1.00	1.00
Tertile 3	176	26 / 150	14.77	1.90 (1.08, 3.33)‡	1.95 (1.09, 3.49)‡
LBW†					
Tertiles 1&2	347	17 / 330	4.90	1.00	1.00
Tertile 3	176	16 / 160	9.09	1.94 (0.96, 3.94)	2.10 (1.00, 4.42)‡

*Model was adjusted for age, pre-pregnant BMI, ethnicity, parity, cigarette smoking and prior LBW (for LBW).

†Birth weight <2500g

‡p<0.05