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Postprandial Free Fatty Acids at Mid-Pregnancy Increase the Risk of Large-for-Gestational-Age Newborns in Women with Gestational Diabetes Mellitus

So-Yeon Kim, Young Shin Song, Soo-Kyung Kim, Yong-Wook Cho, Kyung-Soo Kim

Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

Background: To investigate the association between free fatty acid (FFA) level at mid-pregnancy and large-for-gestational-age (LGA) newborns in women with gestational diabetes mellitus (GDM).

Methods: We enrolled 710 pregnant women diagnosed with GDM from February 2009 to October 2016. GDM was diagnosed by a 'two-step' approach with Carpenter and Coustan criteria. We measured plasma lipid profiles including fasting and 2-hour post-prandial FFA (2h-FFA) levels at mid-pregnancy. LGA was defined if birthweights of newborns were above the 90th percentile for their gestational age.

Results: Mean age of pregnant women in this study was 33.1 years. Mean pre-pregnancy body mass index (BMI) was 22.4 kg/m^2. The prevalence of LGA was 8.3% ($n=59$). Levels of 2h-FFA were higher in women who delivered LGA newborns than in those who delivered non-LGA newborns (416.7 µEq/L vs. 352.5 µEq/L, $P=0.006$). However, fasting FFA was not significantly different between the two groups. The prevalence of delivering LGA newborns was increased with increasing tertile of 2h-FFA (T1, 4.3%; T2, 9.8%; T3, 10.7%; P for trend <0.05). After adjustment for maternal age, pre-pregnancy BMI, and fasting plasma glucose, the highest tertile of 2h-FFA was 2.38 times (95% confidence interval, 1.11 to 5.13) more likely to have LGA newborns than the lowest tertile. However, there was no significant difference between groups according to fasting FFA tertiles.

Conclusion: In women with GDM, a high 2h-FFA level (but not fasting FFA) at mid-pregnancy is associated with an increasing risk of delivering LGA newborns.

Keywords: Birth weight; Diabetes, gestational; Fatty acids; Lipids

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as "diabetes diagnosed during pregnancy that is not clearly overt diabetes" [1]. GDM is steadily increasing. It is becoming an emerging burden in global health [2,3]. GDM has a variety of negative implications for mothers and their offspring. For mothers, it is associated with higher rates of preeclampsia, Cesarean deliveries, shoulder dystocia, and type 2 diabetes mellitus (T2DM) in the postpartum period [4-8]. For offspring born to mothers

with GDM, they have a higher likelihood of developing obesity, having an impaired glucose tolerance, and developing T2DM in childhood or in early adulthood [9,10].

Large-for-gestational-age (LGA) newborn is an important determinant factor in perinatal morbidity and mortality. Women with GDM are more likely to deliver LGA newborns than those without GDM [11]. In general, maternal serum lipid levels will increase during mid to late gestation. Such increase is believed to be beneficial to mother and fetus in terms of lactation and nutrition [12]. It is already known that mater-

Corresponding author: Kyung-Soo Kim https://orcid.org/0000-0002-7738-2284
Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
E-mail: kks982@hanmail.net

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nal fasting serum triglycerides (TG) level at mid-pregnancy can predict LGA newborns independent of maternal pre-pregnancy body mass index (BMI), weight gain during pregnancy, age, and parity in women with GDM [13]. Maternal insulin resistance may link lipid levels and fetal growth in women with GDM. Free fatty acid (FFA) is a fundamental player in insulin resistance. Thus it might be associated with birth weight. However, few studies have examined the association between serum FFA level and LGA newborns in women with GDM. Because LGA newborns have various risks, it is very important to predict LGA during pregnancy. Thus, the aim of this study was to investigate the association between FFA level at mid-pregnancy and LGA newborns in women with GDM.

METHODS

Participants and design

This observational study was conducted in CHA Bundang Medical Center (Seongnam, Korea) from February 2009 to October 2016, enrolling 710 pregnant women aged ≥20 years who were diagnosed with GDM. The diagnosis of GDM was made by a two-step approach. Patients were initially screened with a 1-hour 50-g glucose challenge test as screening at 24 to 28 weeks of gestation. A 3-hour 100-g oral glucose tolerance test (OGTT) was performed for a subset of women who exceeded glucose threshold value (≥140 mg/dL at 1-hour 50-g glucose challenge test). The diagnosis of GDM was made if at least two of four plasma glucose levels (measured fasting and 1, 2, and 3 hours after the 100-g OGTT) met or exceeded glucose threshold value according to the Carpenter and Coustan criteria [14]. Women who were known to have had type 1 diabetes mellitus or T2DM before pregnancy, thyroid disorders, and twin pregnancy were excluded.

At 24 to 32 weeks of gestation (baseline visit), anthropometric assessments were carried out. We also measured blood pressure, and collected venous blood sample, including fasting glucose, glycosylated hemoglobin (HbA1c), lipid profiles, and FFA for all study participants. FFA and TG were also measured at postprandial 2-hour after eating a standard mixed meal (480 kcal, 60% carbohydrate, 20% protein, and 20% fat) composed of Korean food. We collected baseline clinical and demographic characteristics (including a history of obstetric or medical diseases, family history of diabetes, pre-gestational BMI) from medical records. These women were given medical nutrition therapy during their antenatal follow-up. LGA was defined as

birth weight above the 90th percentile for their gestational age based on intrauterine growth percentile curve in Korean 1999 birth cohort [15]. We obtained informed consent from all study participants. This study was approved by the Institutional Review Board of CHA Bundang Medical Center (2017-08-004-001).

Clinical and laboratory measurements

Height and weight were measured for all subjects (wearing minimal clothing without shoes). Blood pressure was measured by trained nurses using an automatic sphygmomanometer after participants were seated for 10 minutes. Serum FFAs were measured by enzymatic colorimetry using a Labospect 008AS (Hitachi, Tokyo, Japan). Reagents used to measure FFAs were acyl-coenzyme A (CoA) synthetase, acyl-CoA oxidase, and 3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline (MEHA). We measured plasma glucose, total cholesterol, TG, and high-density lipoprotein cholesterol (HDL-C) using a Hitachi 7600 analyzer (Hitachi, Tokyo, Japan). We measured HbA1c using a high-performance liquid chromatography (before May 2013, Bio-Rad Variant II, Hercules, CA, USA; after May 2013, Tosoh G8, San Francisco, CA, USA). We assessed C-peptide and insulin levels by chemiluminescence immunoassay (Roche Diagnostic GmbH, Mannheim, Germany). We carried out homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) according to suggested formulas [16].

Statistical analysis

Data for categorical factors are reported as percentages. Continuous variables are presented as mean±standard deviation. Characteristics of participants at baseline were compared using Student's t-test or chi-square test. Subjects were divided into fasting FFA and 2-hour postprandial FFA (2h-FFA) tertiles (T) as follows: fasting FFA T1, ≤603 μEq/L; T2, 604–796 μEq/L; T3, ≥797 μEq/L; 2h-FFA T1, ≤261 μEq/L; T2, 262–400 μEq/L; and T3, ≥401 μEq/L. Pearson's correlation analysis was performed to analyze the correlation between FFA level and various factors after adjusting for age and pre-pregnancy BMI. Binary logistic regression analyses were performed to determine the odds ratio and 95% confidence intervals (CIs) of delivering LGA newborns after adjusting for covariates. All statistical analyses were performed using SPSS version 26.0 (IBM Co., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows baseline characteristics of women with GDM at mid-pregnancy. Mean age was 33.1 years and mean pre-pregnancy BMI was 22.4 kg/m². Among 710 women with GDM, 59 (8.3%) delivered LGA newborns. Women who delivered LGA newborns had higher pre-pregnancy BMI, fasting plasma glucose (FPG), HbA1c, 2h-FFA than those who delivered non-LGA neonates. There were no significant differences in age,

history of GDM, family history of diabetes, parity, gestational weeks, blood pressure, total cholesterol, fasting TG, 2h-TG, fasting FFA, HOMA-IR, HOMA-β, or 100-g OGTT plasma glucose levels between women who delivered LGA and those who delivered non-LGA newborns.

Pregnancy outcomes such as gestational age at delivery, preterm delivery, Cesarean section, and neonate weight were not significantly different among three groups of fasting and 2h-FFA tertile (Table 2). The prevalence of delivering LGA new-

Table 1. Baseline characteristics of women with gestational diabetes mellitus who delivered LGA or non-LGA newborns

Characteristic	Total	Women who delivered non-LGA neonates	Women who delivered LGA neonates	*P* value
Number	710 (100.0)	651 (91.7)	59 (8.3)	
Age, yr	33.1±3.5	33.1±3.5	33.3±3.7	0.646
Pre-pregnancy BMI, kg/m²	22.4±3.8	22.3±3.7	24.1±4.1	<0.001
History of GDM, %	32 (4.5)	29 (4.5)	3 (5.1)	0.743
Family history of diabetes, %	233 (32.8)	208 (32.0)	25 (42.4)	0.103
Parity (% multiparous)	293 (41.3)	264 (40.6)	29 (49.2)	0.199
Gestational weeks	28.1±2.8	28.0±2.9	28.1±1.9	0.842
Systolic blood pressure, mm Hg	111.6±13.5	111.7±13.6	111.4±12.2	0.907
Diastolic blood pressure, mm Hg	68.0±9.4	68.0±9.5	68.3±8.7	0.808
Fasting plasma glucose, mg/dL	88.1±10.7	87.8±10.3	91.8±13.6	0.033
HbA1c, %	5.3±0.4	5.3±0.4	5.4±0.5	0.021
Total cholesterol, mg/dL	246.7±43.0	246.5±42.5	248.5±49.0	0.730
Fasting triglyceride, mg/dL	208.7±93.6	206.6±87.2	231.3±146.6	0.208
2-hour postprandial triglyceride, mg/dL	210.3±98.6	207.9±91.5	236.4±155.9	0.171
HDL-C mg/dL	72.7±13.5	72.6±13.3	73.2±15.8	0.733
Fasting free fatty acid, µEq/L	718.5±228.8	718.6±233.9	717.5±164.5	0.962
2-hour postprandial free fatty acid, µEq/L	357.8±171.9	352.5±170.4	416.7±179.0	0.006
Fasting C-peptide, ng/mL	1.8±0.9	1.8±0.8	1.9±1.0	0.387
Fasting insulin, µU/mL	6.9±5.1	6.8±4.9	7.5±7.0	0.375
HOMA-IR	1.57±1.58	1.55±1.46	1.86±2.53	0.353
HOMA-β	102.8±62.8	103.8±63.5	93.2±53.6	0.217
50-g OGTT, mg/dL	169.1±22.0	168.4±21.6	176.3±24.7	0.009
100-g OGTT				
0 min plasma glucose, mg/dL	96.4±11.6	96.3±11.6	98.0±11.8	0.278
60 min plasma glucose, mg/dL	194.8±27.0	194.4±27.3	198.8±22.8	0.245
120 min plasma glucose, mg/dL	175.11±26.41	174.9±26.5	177.0±26.0	0.576
180 min plasma glucose, mg/dL	145.2±27.4	145.3±27.3	144.2±29.4	0.773

Values are presented as number (%) or mean±standard deviation.
LGA, large-for-gestational-age; BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; OGTT, oral glucose tolerance test.

borns was increased with increasing tertile of 2h-FFA (T1, 4.3%; T2, 9.8%; T3, 10.7%; *P* for trend <0.05) (Fig. 1). However, there was no significant difference in the prevalence of delivering LGA newborns according to tertiles of fasting FFA. In addition, there was no difference in 2h-FFA between women who managed lifestyle modification and those who treated insulin (356.8 μEq/L vs. 362.2 μEq/L, *P*=0.740).

2h-FFA, but not fasting FFA, was positively correlated with

HbA1c after adjusting for age and pre-pregnancy BMI (*r*= 0.096, *P*=0.011) (Table 3). FFA (fasting and 2h) was correlated with total cholesterol and TG (fasting and 2h), but not with HDL-C. Interestingly, although it was not significantly associated after adjusting for age and pre-pregnancy BMI, 2h-FFA was positively correlated with HOMA-IR. On the other hand, fasting FFA was negatively associated with HOMA-IR.

The risk of delivering LGA newborns was 2.66 times (95%

Table 2. Pregnancy outcomes of women with gestational diabetes mellitus according to tertiles of fasting and 2-hour postprandial free fatty acid

Variable	T1	T2	T3	*P* value
Fasting FFA				
Gestational age at delivery, wk	38.4±1.8	38.5±1.7	38.4±1.7	0.897
Preterm delivery[a]	31 (13.4)	27 (11.2)	26 (11.0)	0.678
Cesarean section	89 (49.2)	97 (54.2)	87 (47.8)	0.443
Treatment of GDM				0.698
Diet and exercise	186 (80.2)	199 (82.2)	187 (79.2)	
Insulin	46 (19.8)	43 (17.8)	49 (20.8)	
Neonate weight, g	3,105.4±534.9	3,125.1±479.6	3,110.5±486.6	0.906
2-hour postprandial FFA				
Gestational age at delivery, wk	38.5±1.7	38.4±1.6	38.4±1.9	0.280
Preterm delivery[a]	26 (11.2)	31 (12.7)	27 (11.5)	0.867
Cesarean section	99 (56.3)	89 (49.2)	85 (45.9)	0.136
Treatment of GDM				0.877
Diet and exercise	185 (79.7)	199 (81.6)	188 (80.3)	
Insulin	47 (20.3)	45 (18.4)	46 (19.7)	
Neonate weight, g	3,094.3±507.9	3,117.4±478.0	3,129.4±515.6	0.944

Values are presented as mean±standard deviation or number (%).
T, tertile; FFA, free fatty acid; GDM, gestational diabetes mellitus.
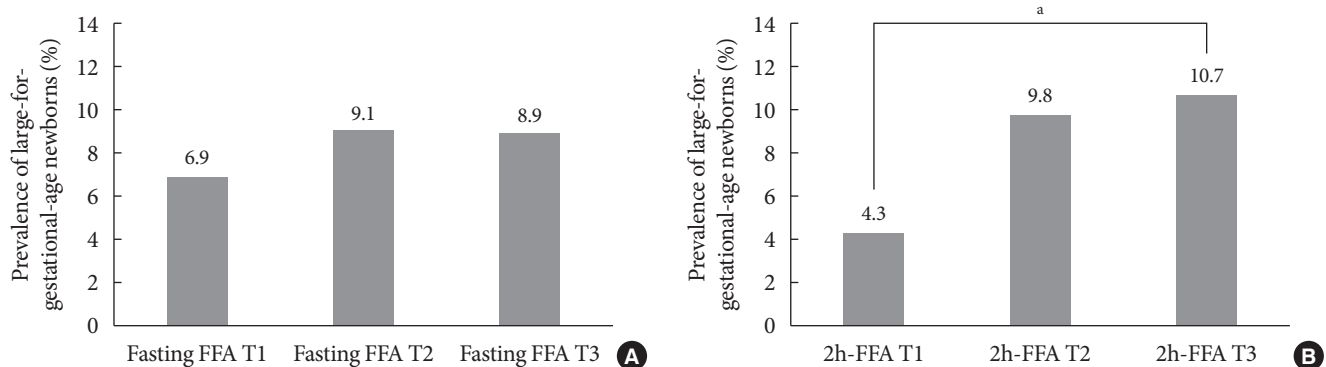[a]Preterm delivery information was missing for 168 participants.

Fig. 1. Prevalence of large-for-gestational-age newborns according to the tertile (T) of fasting (A) and 2-hour (2h) postprandial (B) free fatty acid (FFA) level. [a]*P* for trend <0.05.

Table 3. Correlation of fasting and 2-hour postprandial free fatty acid levels with variables

Variable	Fasting FFA				2-hour postprandial FFA			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	r	P value	r	P value	r	P value	r	P value
Fasting plasma glucose, mg/dL	−0.195	<0.001	−0.212	<0.001	−0.007	0.859	−0.045	0.241
HbA1c, %	0.053	0.156	0.045	0.234	0.125	0.001	0.096	0.011
Total cholesterol, mg/dL	0.069	0.065	0.091	0.017	0.068	0.070	0.095	0.012
Fasting triglyceride, mg/dL	0.207	<0.001	0.214	<0.001	0.297	<0.001	0.292	<0.001
2-hour postprandial triglyceride, mg/dL	0.163	<0.001	0.168	<0.001	0.327	<0.001	0.319	<0.001
HDL-C, mg/dL	0.026	0.496	0.033	0.378	−0.070	0.062	−0.058	0.127
Fasting C-peptide, ng/mL	−0.057	0.126	−0.082	0.032	0.147	<0.001	0.104	0.006
Fasting insulin, μU/mL	−0.064	0.088	−0.091	0.017	0.082	0.029	0.030	0.435
HOMA-IR	−0.067	0.073	−0.091	0.017	0.077	0.039	0.031	0.412
HOMA-β	0.090	0.017	0.084	0.027	0.103	0.006	0.068	0.073

Adjusted by age and pre-pregnancy body mass index.
FFA, free fatty acid; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.

Table 4. Odds ratios for predictors of large-for-gestational-age newborns

Characteristic	Model 1 (95% CI)	P value	Model 2 (95% CI)	P value	Model 3 (95% CI)	P value
Fasting FFA						
1st tertile	1.00		1.00		1.00	
2nd tertile	1.35 (0.69–2.64)	0.381	1.40 (0.71–2.76)	0.333	1.49 (0.75–2.95)	0.256
3rd tertile	1.32 (0.67–2.60)	0.423	1.30 (0.66–2.58)	0.453	1.43 (0.71–2.86)	0.317
2-hour postprandial FFA						
1st tertile	1.00		1.00		1.00	
2nd tertile	2.42 (1.13–5.18)	0.023	2.25 (1.04–4.84)	0.039	2.27 (1.05–4.90)	0.037
3rd tertile	2.66 (1.25–5.66)	0.011	2.37 (1.10–5.09)	0.027	2.38 (1.11–5.13)	0.027

Model 1: unadjusted; Model 2: adjusted by age and pre-pregnancy body mass index; Model 3: adjusted by age, pre-pregnancy body mass index, and fasting plasma glucose.
CI, confidence interval; FFA, free fatty acid.

CI, 1.25 to 5.66) higher in the highest tertile of 2h-FFA compared with that in the lowest tertile (Table 4). Even after adjusting for age, pre-pregnancy BMI, and FPG, the risk of delivering LGA newborns was still 2.38 times (95% CI, 1.11 to 5.13) higher in the highest tertile of 2h-FFA. The cut-off value of 2h-FFA for predicting LGA newborns was 343.5 μEq/L and its sensitivity and specificity were 66.1% and 59.0%, respectively (Supplementary Table 1). However, there was no significant difference for the risk of delivering LGA newborns among tertiles of fasting FFA.

DISCUSSION

LGA newborns are common in women with GDM. They should be carefully managed because various metabolic disorders can be developed later in life [11]. Many risk factors have been investigated for delivering LGA newborns in women with GDM. However, few studies have evaluated the association between FFA level at mid-pregnancy and LGA newborns. In this study, we found that a high 2h-FFA level, but not fasting FFA, at mid-pregnancy was associated with an increasing risk of delivering LGA newborns in women with GDM.

LGA is a risk factor for complications among both newborns and mothers [17,18]. For infants, LGA has been associated with increased risks of infant mortality and traumatic injuries during delivery [19,20]. These traumatic injuries include shoulder dystocia, clavicle or humerus fractures and brachial or facial paralysis [21,22]. High birth weight is also extended to adverse consequences in later life, including later development of overweight [23]. For mothers, delivering LGA newborns is associated with genital tract injury, prolonged labor, risk of postpartum bleeding, and an increased risk of cesarean delivery [18,20,22]. Because GDM is an important risk factor of delivering LGA, proper screening and medical care for LGA in women with GDM are likely to be important.

To date, many risk factors for delivering LGA newborns have been identified, such as advanced maternal age, obesity, multiparity, gestational weight gain, smoking, and GDM [24-26]. A Swedish population-based cohort study of 1,260,297 women has reported that women with GDM have 3.4 times higher risk of delivering LGA newborns than women without GDM [11]. In general, fetal growth is determined not only by plasma glucose levels, but also by other fuels such as lipids and amino acids [27]. Several studies have found that maternal lipids are associated with fetal growth [28,29]. It is well known that maternal TG concentration is independently associated with LGA newborns [13,30-32]. In this study, however, there was no difference in maternal TG concentration (fasting and 2h) between women who delivered LGA and those who delivered non-LGA newborns, unlike FFA levels. There may be several reasons, such as ethnic characteristics, variability of measurements, etc., but not all of them are certain. Because FFA as fundamental lipid is an essential component of lipid metabolism and insulin resistance, we could assume that FFA might be associated with LGA newborns in women with GDM. We evaluated the association between FFA (fasting and 2h) and LGA newborns and found that only 2h-FFA was associated with elevated risk of LGA newborns in women with GDM. However, as opposed to our expectation, 2h-FFA was not significantly associated with HOMA-IR. This might be because HOMA-IR values were relatively low (mean 1.57) compared with those in Western populations due to low pre-pregnancy BMI (mean 22.4 kg/m^2).

FFAs are lipids bound to transport protein, such as albumin. They are also known as non-esterified fatty acids [33]. FFAs play a critical role in the development of T2DM possibly due to lipotoxicity defined as cellular dysfunction caused by elevated level of FFAs [34], thereby reducing glucose uptake by peripheral tissues and stimulation of endogenous glucose production [35]. Several studies have shown higher plasma levels of FFA in T2DM and obesity [36-39]. Hawkins et al. [39] have found that plasma FFA concentrations were higher in individuals with poor glycemic control than in individuals with good glycemic control and nondiabetic individuals during euglycemia (poor glycemic control, 400±95 μmol/L; good glycemic control, 237±28 μmol/L; nondiabetic individuals, 170±28 μmol/L; $P<0.01$). During hyperglycemia, FFA concentrations were also higher in individuals with poor glycemic control than other two groups (poor glycemic control, 381±75 μmol/L; good glycemic control, 198±19 μmol/L; nondiabetic individuals, 170±28 μmol/L; $P<0.01$). In addition, plasma FFA levels are commonly increased during late gestation [40]. They are responsible for much of physiologic insulin resistance that occurs in all women during the 2nd half of normal pregnancy [40]. Because fetal birth weight is mainly associated with maternal insulin resistance and lipid metabolism, FFA might be a crucial role for LGA newborns. However, how FFA, especially 2h-FFA, influences fetal growth has not been sufficiently investigated yet.

Inappropriately increased plasma FFA levels could have adverse metabolic effects such as reduced glucose uptake by peripheral tissues and stimulation of endogenous glucose production [35,36]. Some reviews have suggested that detrimental effects of elevated FFAs are likely to be more severe in a postprandial state than in a fasting state [41,42]. Wang et al. [43] have also suggested that higher concentrations of 2h-saturated fatty acid (SFA), not fasting SFA, are independently associated with an increased risk of T2DM. The postprandial state is vital because it not only represents an early metabolic response to glucose, meals, or nutrients, but also accounts for the most time spent in meal sequence during daytime and the usual long duration of certain postprandial metabolites such as the periods for lipids and fatty acids [44]. The ability to regulate postprandial metabolites and decrease blood glucose is apparently a crucial reflection of metabolic efficiency. In addition, previous studies have found that an exacerbated accumulation of 2h-SFA is involved in insulin resistance [45,46]. Therefore, it is likely that increased 2h-FFA levels in women with GDM might have detrimental effects regarding the risk of delivering LGA newborns due to increased insulin resistance. In this study, we found that the prevalence of delivering LGA newborns was increased in women with high 2h-FFA, rather than

with high fasting FFA.

Some limitations need to be considered when interpreting our findings. First, 2h-FFA was measured after eating a standard mixed meal, not a 75-g OGTT. Second, as our study participants were confined to Korean women with a singleton pregnancy, we could not generalize these results to other ethnic populations. Third, because we could not get the data of known risk factors for LGA newborns such as smoking history and gestational weight gain, we could not evaluate the association between FFA and LGA newborns after adjustment for aforementioned factors. Finally, we only measured serum FFA once at mid-pregnancy. Thus we could not evaluate effects of dynamic changes of FFA during pregnancy.

In conclusion, a high 2h-FFA level (but not a high fasting FFA) at mid-pregnancy is associated with an increasing risk of delivering LGA newborns in women with GDM. Consequently, we should try to prevent excessive fetal growth if women with GDM have high 2h-FFA levels at mid-pregnancy.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0023.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: S.Y.K., K.S.K.
Acquisition, analysis, or interpretations of data: S.Y.K., Y.S.S., S.K.K., Y.W.C., K.S.K.
Drafting the work or revising: S.Y.K., Y.S.S., S.K.K., Y.W.C., K.S.K.
Final approval of the manuscript: S.Y.K., Y.S.S., S.K.K., Y.W.C., K.S.K.

ORCID

So-Yeon Kim *https://orcid.org/0000-0002-8858-7840*
Kyung-Soo Kim *https://orcid.org/0000-0002-7738-2284*

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Supplementary Table 1. Cutoff value, sensitivity, specificity, and AUC of the 2h-FFA for predicting large-for-gestational-age newborns

	Cut-off level, μEq/L	Sensitivity, %	Specificity, %	AUC (95% CI)
2h-FFA	343.5	66.1	59.0	0.618 (0.546–0.690)

AUC, area under the curve; 2h-FFA, 2-hour postprandial free fatty acid; CI, confidence interval.