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ORIGINAL ARTICLE

Prediction of Neonates' Macrosomia with Maternal Lipid Profile of Healthy Mothers

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Key Words
fetal macrosomia;
gestational diabetes mellitus;
large for gestational age;
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Background: The aim of this study is to identify the association between the lipid profile of healthy nondiabetic, nonobese pregnant women in the first weeks of the third trimester of pregnancy and macrosomia or large-for-gestational-age (LGA) neonates with normal pregnancies.
Materials and methods: In this cohort study, 200 pregnant healthy women without gestational diabetes mellitus (GDM), obesity, or hypertension and carrying a single fetus in a prenatal clinic of a referral hospital were included based on a convenience sampling. Then, we took a blood sample to assess fasting blood sugar (FBS), triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). GDM was assessed after administering 50 g of oral glucose. All cases were followed until the end of pregnancy. The main outcome measurement was neonatal birth weight.
Results: Only 154 mothers met eligibility criteria. There were eight cases (5.2%) with macrosomia (birth weight $\geq$ 4000 g) and 35 cases (22.7%) with LGA. Linear regression showed that

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mothers' TG and neonates' gender were independent predictors of the birth weight of the children (R-square = 0.52, $p < 0.001$). Logistic regression analysis showed that maternal FBS and TG are the most independent variables which can predict the presence of macrosomia (Nagelkerke R-square = 0.53, $p < 0.001$) and maternal TG and child gender are the most independent variables that can predict the presence of LGA in neonates of a healthy mother (Nagelkerke R-square = 0.49, $p < 0.001$).

Conclusion: Maternal triglyceride levels may be a significant predictor of fetal size in late pregnancy but not in early pregnancy. Our study reinforces that this is true not only in the case of macrosomia (birth weight > 4500 g), but also for LGA.

1. Introduction

Macrosomia is a common morbidity that may result in complications for mother and neonate. Even though fetal macrosomia occurs more often in pregnancies of diabetic mothers, considerable numbers of infants with macrosomia are born from nondiabetic mothers (8–14%).[1] The rate of newborns of large size in many countries is increasing.[2] Diabetes is a known cause of macrosomia.[3] However, 80% of infants with macrosomia are born to mothers who do not have hyperglycemia, and various factors have been associated with this occurrence.[4] In addition, some studies have attempted to find a suitable index that can predict macrosomia in mothers who are not diabetic,[5–8] and other studies have examined newborns of groups of mothers with and without gestational diabetes mellitus (GDM).[9–11]

Clausen et al[12] have assessed the risk of macrosomia in relation to early second trimester maternal serum lipids; in the current study, we have focused on maternal serum lipids during the first weeks of the third trimester of pregnancy. This is because the possibility of developing a late impaired glucose metabolism after the screening time in some of the mothers could not be excluded.[13]

There are also known risk factors for macrosomia, including maternal fasting glycemia, body mass index (BMI) prior to pregnancy, and hemoglobin (Hb) A1c.[3] In the current study, we used healthy nondiabetic, nonobese, and normotensive pregnant women to focus on the remaining risk factors after restricting our study to such normal mothers. Maternal factors explain approximately 50% of the variance in birth weight, whereas paternal factors have no significant effect.[4] Growth of the fetus depends on nutrients such as glucose, lipids, and amino acids.[1] The respective roles of lipids, amino acids, hormones such as leptin, and growth factors need to be evaluated.[4]

Therefore, in this study we evaluated the association between metabolic characteristics, especially lipid profile, of the healthy nondiabetic, nonobese pregnant women in the first weeks of the third trimester of the pregnancy and macrosomia or large-for-gestational-age (LGA) neonates with normal pregnancies.

2. Materials and Methods

In this cohort study, we assessed 200 pregnant women who were referred to the prenatal clinic of the Shahid Akbar Abadi Hospital (one of the main referral hospitals in Tehran, capital of Iran), between 2010 and 2011. All women were generally healthy pregnant women carrying a single fetus, between 25 weeks and 32 weeks of their gestational age, BMI between 17.5 kg/m^2 and 29 kg/m,^{2} without a history of diabetes prior to or during previous pregnancies and with a negative result from the diabetes screening test in the current pregnancy, hypertensive disease and preeclampsia, thyroid diseases, lupus, antiphospholipid antibody syndrome, and other collagen vascular diseases. Our exclusion criteria were preterm labor prior to 37 weeks of gestational age and any abnormality or disorder in the fetus or neonate.

Sampling method was based on convenience method. After including cases that met the eligibility criteria and obtaining written informed consent, we took a blood sample for checking fasting blood sugar (FBS), triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) after 10-12 hours of fasting. Then, 50 g oral glucose was administered for screening GDM and serum glucose was evaluated after 1 hour. GDM was defined as FBS higher than 90 mg/dL and 1 hour glucose tolerance test after 50 g oral glucose higher than 130 mg/dL. Cases with GDM or impaired glucose tolerance test (GTT) were excluded from the study. All cases were followed until the end of pregnancy. At this time, gestational age, complications during pregnancy, and eligibility criteria were assessed. We gathered data about gender and birth weight of the neonates after birth. Macrosomia was defined as neonate birth weight higher than 4000 g. LGA was defined as neonate's birth weight higher than 3412 g for infants at 38 weeks of gestational age, 3622 g for infants at 39 weeks of gestational age, 3798 g for infants at 40 weeks of gestational age, and 3930 g for infants at 41 weeks of gestational age. This definition was according to the neonates' weight higher than 75% of their predicted value according to their gestational age.[14] Blood glucose was measured by oxidase method and lipid profiles by enzyme-linked immunosorbent assay method. BMI was defined as kg/m^2.

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± standard deviation (SD), minimum and maximum value (range), and frequencies. The significance of the differences between the study groups was tested using the *t* test. Differences in categorical variables were tested using a Chi-square test. Associations between quantitative variables (maternal metabolic parameters and birth

weight) were analyzed using Pearson correlation coefficients. Partial correlation was also done for eliminating the confounder effect of other variables and determining the main effect of the variable under study (here TG). Stepwise linear regression analysis was performed to find independent predictors for birth weight in the study group. Odds ratios (ORs) and 95% confidence interval (95% CI) were evaluated by forward stepwise logistic regression analyses. We entered all variables with $p < 0.2$ in a logistic model. Moreover, we entered variables which other studies considered as associated with macrosomia/LGA or variables that most studies have entered in their regression models. Therefore, the results of our logistic models are comparable with similar studies because the results are relatively adjusted for the same confounders. A p value < 0.05 was considered statistically significant in all statistical tests. We also categorized quantitative variables (with significant association with LGA) according to their quartiles. Then, we assessed the dose-response relation of these with LGA. By this analysis, we were seeking one criteria of Hill for causality.

The ethics committee of the Tehran University of Medical Sciences approved the protocol of the study. All mothers signed a written informed consent form.

3. Results

In this study, 200 cases were included. There were 21 cases (10.5%) with preterm labor prior to the 37th week of gestational age, eight cases (4%) with hypertension during pregnancy, one case (0.5%) of fetal death due to the mother's anaphylactic shock, and 16 cases (8%) with change in address and telephone numbers that were lost to follow-up. Basic characteristics of lost cases were not different from the other cases. Therefore, we analyzed the results of the 154 remaining normal mothers. Their mean age and BMI prior to pregnancy were 26.6 ± 5.2 years and 22.6 ± 2.3 kg/m^2, respectively. There were eight cases (5.2%) with macrosomia, 35 cases (22.7%) with LGA, and 77 cases (50%) with nulliparity. Their FBS levels were also normal. Lipid profile was not normal in all cases (Table 1).

Forty-six percent and 8% of neonates were male. Their gestational age was between 38 weeks and 41 weeks, with an average of 39.3 ± 0.92 weeks. Birth weight of the children was 3241.9 ± 463.8 kg. Male children had significantly higher birth weight ($p < 0.001$; Table 1). Birth weight of the children was correlated with higher total cholesterol ($r = 0.50$, $p < 0.001$), LDL ($r = 0.40$, $p < 0.001$), TG ($r = 0.68$, $p < 0.001$), and lower HDL ($r = -0.47$, $p < 0.001$) (Table 1).

Partial correlation showed when we controlled for either total cholesterol ($r = 0.54$, $p < 0.001$), LDL ($r = 0.60$, $p < 0.001$), or HDL ($r = 0.56$, $p < 0.001$); birth weight of the children is again correlated with TG. Stepwise linear regression showed that mothers' TG and neonates' gender were independent predictors of the birth weight of the children (R-square = 0.52, $p < 0.001$). The model shows that 52% of the neonates' birth weight can be predicted according to the changes of the mothers' TG and neonates' gender. The model also shows that the effect of mothers' TG during first half of the third trimester in predicting birth weight of the children is more than twofold in comparison with neonates' gender. Each unit increase in mothers' TG will increase the birth weight of the neonates by 5.24 g and male gender will cause such increase to be 238.81 g when the other variable is constant (Table 2).

Forward stepwise logistic regression analysis showed that maternal FBS and TG are the most independent variables that can predict the presence of macrosomia (birth weight ≥ 4000 g) in neonates of healthy mothers (nondiabetic, normal BMI, without hypertension, and with term single fetus pregnancy; Nagelkerke R-square = 0.53, $p < 0.001$). To be able to compare the importance of FBS and triglyceride we computed their z-score and substituted their z-score for their crude value in logistic model. Therefore, the analysis showed that TG has a more important role in predicting the value of a neonate's birth weight because z-score of maternal TG and FBS has OR (95% CI) equal to 9.44 (2.86–31.16) and 3.09 (1.006–9.48), respectively. Mothers' TG and FBS in gestational weeks between 25 and 32 have a more important role than other variables in predicting birth weight of the neonates. Each unit increase in mothers' FBS during the first half of the third trimester of the pregnancy will cause a 1.24 increase in the

Table 1 Basic characteristics of the mothers and their neonates.

Variables			Value
Mother			
Demographics	Age, y		26.6 ± 5.17, 16/40
	Parity		1.7 ± 0.79, 1/4
	Weight prior to pregnancy, kg		59.7 ± 5.76, 50/75
	Height, cm		162.6 ± 4.8, 150/170
	BMI prior to pregnancy, kg/m^2		22.6 ± 2.3, 17.7/28.6
	Weight gain during pregnancy, kg		11.6 ± 2.69, 7/20
	Gestational age at the time of blood sampling, wk		30 ± 2.1, 25/32
Biochemistry	FBS, mg/dL		81 ± 5.14, 67/90
	Total cholesterol, mg/dL		201.4 ± 38.4, 110/300
	LDL, mg/dL		115.3 ± 34.9, 38/204
	HDL mg/dL,		46.6 ± 4.36, 37/61
	Total triglyceride, mg/dL		197.5 ± 51.9, 70/350
Child			
Demographics	Gender	Male	72 (46.8)
		Female	82 (53.2)
	Birth weight, g	Male	3476.1 ± 413.7, 2400/4130
		Female	3036.2 ± 405.9, 2000/4100

Data are presented as mean ± SD, min/max or *n* (%).
BMI = body mass index; FBS = fasting blood sugar; HDL = high-density lipoprotein; LDL = low-density lipoprotein; max = maximum; min = minimum; SD = standard deviation.

Table 2 Predictors of the birth weight of the neonates.

Independent variable	Unstandardized coefficients		Standardized coefficients Beta	Sig.
	B	SE		
Triglyceride	5.24	0.54	0.59	< 0.001
Male gender of the child	238.81	56.08	0.26	< 0.001

B = beta; SE = standard error; Sig = significance.

odds of macrosomia of the neonate. Each unit increase in TG will add 0.044 the odds of macrosomia of the neonate (Table 3). We should note that if z-scores are not taken into consideration, crude values will mislead us in ranking which independent variable is more important. This issue was not considered in any previously published similar studies in the field.

Forward stepwise logistic regression analysis showed that mother's TG and child gender are the most independent variables which can predict the presence of LGA (birth weight according to gestational age as mentioned above) in neonates of a healthy mother (Nagelkerke R- square = 0.49, $p < 0.001$). Table 4 shows that the mother's TG in gestational weeks between 25 and 32 and child gender have more important roles than other variables in predicting birth weight of the neonates. We computed the z-score of maternal TG to be able to compare the importance of maternal TG and neonate's gender in predicting LGA in neonates. Adjusted OR of the z-score of the maternal TG was 5.90 (95% CI: 2.68-13.00).

The mother's age, BMI, parity, and birth (gestational) age had no significant association with LGA. For evaluating dose-response relation of significantly correlated variables with LGA, we divided quantitative variables according to their quartiles. As we can see, there was no dose- response relationship in most variables. This may be due to our eligibility criteria whereby we only entered cases without significant diseases in past medical history and without GDM, obesity, and hypertension. Only lipids and high weight gain were associated with LGA in comparison with their baseline characteristics, which was the lowest group in all variables except for HDL in which the control group showed the highest HDL level (Table 5).

4. Discussion

In this study, we evaluated the role of lipid profile of pregnant women in the first weeks of the third trimester to better estimate the birth weight of neonates prior to birth. This time of checking enabled us to check late impaired glucose metabolism after the usual screening time in pregnant women. Such a prediction can aid in the diagnosis of macrosomia and LGA some weeks earlier than normal and can even help to reverse the mechanism of such problems by controlling the most independent important factor, being TG in both linear and logistic regression models, for preventing birth, childhood, and adulthood complications in apparently healthy-appearing non-diabetic, nonobese, normotensive mothers. The interesting finding was the direct effect of FBS on macrosomia even in normal pregnancies of nondiabetic, nonobese mothers. However, the effect of FBS was lower than TG on macrosomia.

According to regression models, all lipids play a probable role in birth weight via TG. Male gender is also an important independent factor showing the inevitable role of hormonal and genetic components. The real role of maternal hyperlipidemia in fetal growth is not completely understood. However, fasting maternal TG level between 24 weeks and 32 weeks of gestation has been directly correlated with birth weight increase at term. This effect is independent from the effect of the mother's obesity, weight gain during pregnancy, and maternal FBS level during pregnancy in various studies as well as the current one.[15–17]

Other studies have shown a maternal lipid level increment in the second half of gestation.[11, 18–20] In women with GDM, TG is also associated with birth weight after adjustment for gestational age.[21] In our study, regression models for LGA are also adjusted for gestational age, because our definition for LGA is according to gestational age. A similar Indian study showed the relative risk of having heavier babies weighing 3.5 kg or greater was 2 (95% CI: 0.9–4.2) for women with hypertriglyceridemia and 2.6 (95% CI: 0.78–8.4) when controlled for fasting glucose, BMI, and pregnancy weight gain. When studied together, the combination of hypertriglyceridemia, fasting hyperglycemia, and higher BMI was a significant predictor of heavier neonates with RR = 9.7 (95% CI: 1.7–62.6).[20] In a study of 85

Table 3 Predictors of macrosomia in the neonates.

Independent variables *	B	SE of B	Sig.	Adjusted OR	95% CI for OR	
					Lower	Upper
FBS	0.22	0.11	0.049	1.245	1.001	1.55
Triglyceride	0.04	0.01	< 0.001	1.044	1.02	1.07

B = beta; CI = confidence interval; FBS = fasting blood sugar; OR = odds ratio; SE = standard error; Sig = significance.
* Adjusted for mother's age, weight prior to pregnancy, FBS, and cholesterol.

Table 4 Predictors of large for gestational age in the neonates.

Independent variables *	B	SE of B	Sig.	Adjusted OR[a]	95% CI for OR	
					Lower	Upper
Child male gender	1.45	0.57	0.011	4.275	1.40	13.04
Mother's TG	0.03	0.01	< 0.001	1.035	1.02	1.05

B = beta; CI = confidence interval; OR = odds ratio; SE = standard error; Sig = significance.
* Adjusted for mother's age, weight prior to pregnancy, FBS, and cholesterol.

Table 5 Risk of LGA in relation to mothers' metabolic and anthropometric factors' quartiles.

Maternal factors	All	LGA cases, *n* (%)	OR (95% CI) unadjusted	aOR (95% CI)*
Weight prior to pregnancy				
Q1: <55	36	7 (19.4)	1	1
Q2: 55–59.9	35	11 (31.4)	1.9 (0.6–5.7)	1.04 (0.27–4.1)
Q3: 60–64.9	43	10 (23.3)	1.3 (0.4–3.7)	0.53 (0.12–2.38)
Q4: ≥65	40	7 (17.5)	0.88 (0.28–2.8)	0.45 (0.1–2.1)
Height				
Q1: <159.75	38	10 (26.3)	1	1
Q2: 159.75–162.9	35	7 (20)	0.7 (0.2–2.1)	0.84 (0.21–3.37)
Q3: 163–166.9	39	5 (12.8)	0.4 (0.1–1.3)	0.16 (0.03–0.9)
Q4: ≥167	42	13 (31)	1.3 (0.5–3.3)	1.1 (0.29–3.9)
Weight gain				
Q1: ≤9	45	6 (13.3)	1	1
Q2: 9.1–11.74	32	6 (18.8)	1.5 (0.4–5.2)	1.3 (0.25–6.8)
Q3: 11.75–13	41	8 (19.5)	1.6 (0.5–5)	1.5 (0.4–6.4)
Q4: > 13	36	15 (41.7)	**4.6 (1.6–13.7)**	**4.5 (1.01–20.2)**
Total cholesterol				
Q1: ≤172	39	2 (5.1)	1	1
Q2: 172.1–199.9	35	6 (17.1)	3.8 (0.7–20.4)	2.3 (0.4–15.2)
Q3: 200–234.9	37	9 (24.3)	**5.9 (1.2–29.7)**	1.2 (0.2–8.6)
Q4: ≥235	43	18 (41.9)	**13.3 (2.8–62.5)**	1.1 (0.2–8.1)
LDL				
Q1: ≤88	38	3 (7.9)	1	1
Q2: 88.1–113	40	9 (22.5)	3.4 (0.8–13.6)	2.04 (0.4–10.9)
Q3: 113.1–143.9	37	10 (27)	**4.3 (1.1–17.3)**	0.6 (0.1–4.03)
Q4: ≥144	39	13 (33.3)	**5.8 (1.5–22.6)**	0.8 (0.1–4.4)
HDL				
Q1: ≤43	40	18	**16.4 (3.5–77.2)**	0.6 (0.07–5.3)
Q2: 43.1–46	37	10	**7.4 (1.5–36.5)**	0.7 (0.08–5.6)
Q3: 46.1–49.9	35	5	3.3 (0.6–18.4)	1.7 (0.2–11.6)
Q4: ≥50	42	2	1	1
Triglyceride				
Q1:<170	37	2 (5.4)	1	1
Q2: 170–199.9	37	0	0	0
Q3: 200–229.9	37	6 (16.2)	3.4 (0.6–18)	3.2 (0.5–20.7)
Q4: ≥230	43	27 (62.8)	**29.5 (6.2–139.6)**	**28.2 (3.5–230.3)**
FBS				
Q1: <78	35	9 (25.7)	1	1
Q2: 78–80.9	36	11 (30.6)	1.3 (0.4–3.6)	3.6 (0.8–16.3)
Q3: 81–84.9	42	5 (11.9)	0.4 (0.1–1.3)	0.5 (0.1–2.4)
Q4: ≥85	41	10 (24.4)	0.9 (0.3–2.6)	0.9 (0.2–3.6)

aOR = adjusted odds ratio; CI = confidence interval; FBS = fasting blood sugar; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LGA = large for gestational age; OR = odds ratio; Q = quartile.
Bold numbers show significant ORs.
* Variables in model: mother's age, weight prior to pregnancy, FBS, triglyceride, cholesterol, and child gender. If the categorical variable was one of these confounders or had colinearity with other variables, we excluded that variable and only the categorical variable was entered.

healthy mothers in Greece, children born LGA of mothers without confirmed impaired glucose tolerance during pregnancy ($n = 37$) showed higher insulin concentrations than children appropriate for gestational age (AGAs, $n = 48$).[5] In our study, FBS was also a predictor of macrosomia. Another similar cohort study of 2050 pregnancies in Norway demonstrated that maternal TG in the first half of pregnancy (early second trimester) was also associated with a risk of macrosomia (birth weight $>$ 4500 g).[12] Many previous studies have shown that diabetes or FBS are independent risk factors for macrosomia.[1,3,6,9,12,17,19] However, few studies have focused on cases without DM,[5–8] a subgroup that has a higher proportion in comparison with patients with diabetes or hypertension. Our target population is these normal women.

In an Italian study on 180 pregnant Caucasian women, 83 women with normal glucose tolerance were evaluated. Prepregnancy BMI and fasting maternal serum TG determined in the last trimester of gestation were independently associated with neonatal birth weight in women with normal glucose tolerance, but a positive screening test. TG levels measured in the third trimester of pregnancy are independent of the genetic polymorphism of ApoE.[11]

Another similar study in Japan on 146 women showed that midpregnancy maternal fasting triglyceride level at 24–32 weeks (hypertriglyceridemia over 259 mg/dL) was the significant predictor of LGA infants, independent of prepregnancy BMI, maternal weight gain, and maternal plasma glucose levels (OR = 11.6, 95% CI: 1.1–122; $p = 0.04$) according to logistic regression analysis.[22] A study on mothers with gestational diabetes demonstrated that birth weight of the largest offspring, maternal fasting glycemia, BMI prior to pregnancy, HbA1c, and TG at booking were independent predictors of a birth weight according to their strength. All of these predictors, except TG concentrations, remained significant when gestational age at diagnosis was entered into models.[3] A study found that triglycerides and non-HDL cholesterol were correlated to placental weight. It is therefore possible that the metabolic changes associated with maternal overweight may promote placental growth.[12]

Compared to the large sample or heterogeneous samples of previous studies, we have a very homogenous sample without diabetes, hypertension, obesity, and preterm labor. This may be the reason that our standard deviations are not large in most metabolic and anthropometric characteristics of participants. Moreover, our relatively small sample let us to do tests during fasting. This increases both the validity and homogeneity of the data and decreases type 2 error as in some other studies.[12] Physicians decide for their patients according to these standard data (fasting values of weight, FBS, TG, and cholesterol); therefore, it increases the practicality of the results.

The normal homogenous population in the current study excludes discrepancies due to different diseases such as diabetes and hypertension, and also different strategies for treatment of such diseases and makes our sample as homogenous as possible. This may decrease the generalizability of our data to all real cases, as some of the real cases have diseases such as diabetes and hypertension; however, it increases the comparability of our results with studies in which all or some proportion of their sample is healthy pregnant women with babies of normal term. External validity (representativeness) of our data in healthy women is high because this group of women has a very similar definition for normal levels of blood chemistry and has no diseases across different countries. In addition, controlling for confounders that may distort the results increases the homogeneity of the population under study and representativeness of the findings. In its best situation, our data can be reproducible only in healthy women.

A high maternal triglyceride level prior to 20 weeks of gestation was not an independent risk factor for macrosomia (birth weight $>$ 4500 g) in some studies,[5,12] but it was related to birth weight in some other studies.[3] However, it was independently correlated to birth weight between 24 weeks and 28 weeks of gestation, even after adjustment for maternal BMI[22] and also obesity.[23] Thus, maternal triglyceride levels may be a significant predictor of fetal size in late but not in early pregnancy. Our study reinforces that this is true not only for macrosomia (birth weight $>$ 4500 g) but also for LGA.

In conclusion, maternal triglyceride levels may be a significant predictor of fetal size in late pregnancy but not in early pregnancy.

Conflicts of Interest

The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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