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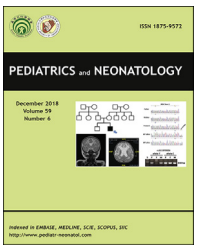

Original Article

# Level of maternal triglycerides is a predictor of fetal macrosomia in non-obese pregnant women with gestational diabetes mellitus

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**Key Words**
birth weight;
fetal macrosomia;
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pregnancy;
triglycerides

**Abstract** *Background:* The role of maternal serum triglycerides (TGs) in the development of fetal macrosomia in different subgroups of body mass index (BMI) has received little attention. The aim of this study was to determine the association between the level of maternal TGs and fetal macrosomia in Iranian pregnant women of different BMI subgroups with gestational diabetes mellitus (GDM).

*Methods:* This cohort study was conducted on 305 pregnant women with GDM referred for glucose control to Kowsar Hospital in Qazvin, Iran. Level of TGs was measured on the 24th–28th weeks of pregnancy. The ROC curve of the level of TGs was depicted in BMI subgroups to predict fetal macrosomia. Logistic regression analysis was used to determine the risk of macrosomia per 1-SD increase in the level of TGs.

*Results:* The prevalence of hypertriglyceridemia did not significantly differ across BMI subgroups. Macrosomia was more prevalent in obese women (32.2%) than overweight (19.1%) and normal weight (11.1%) women ($P < 0.05$). A 1-SD increase in the level of TG was associated with 4.2 and 1.9 times increased risk of macrosomia in normal weight ($P < 0.01$) and overweight ($P < 0.01$) women, respectively. Serum level of TGs was not associated with macrosomia in any adjustment models in obese women. The area under the curve of the level of TGs for macrosomia was 0.828 (95% CI: 0.712–0.911, $P < 0.001$) and 0.711 (95% CI: 0.639–0.775, $P < 0.001$) in normal weight and overweight women, respectively.

*Conclusion:* Hypertriglyceridemia was a predictor of macrosomia in non-obese women. More studies on different ethnicities and lifestyles are necessary to determine the association between the level of maternal TG and fetal macrosomia in BMI subgroups.

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## 1. Introduction

Macrosomia is the main complication of gestational diabetes mellitus (GDM), associated with important neonatal complications such as birth trauma, hypoglycemia, and hematologic and respiratory complications.[1,2] The complications of macrosomia are not limited to the neonatal period and fetal macrosomia is a major risk factor for obesity and type 2 diabetes mellitus in adolescence and young adulthood.[3]

For decades, the occurrence of macrosomia has been attributed to high maternal blood glucose. With regards to the Pedersen hypothesis, excess maternal glucose transfers through the placenta and stimulates islet cells and hyperinsulinemia, resulting in macrosomia.[4]

Although macrosomia has been associated with maternal blood glucose,[5,6] the results of previous studies are inconsistent.[7,8] Despite appropriate glycemic control in many pregnant women with GDM, macrosomia is still prevalent and is often linked to unrecognized maternal hyperglycemia. However, the risk of macrosomia is higher in well controlled GDM confirmed by continuous glucose monitoring (CGM) than the general population.[9] The association between fetal macrosomia and age, obesity, previous history of macrosomia, and hypertriglyceridemia has been showed previously.[10]

The association between maternal hypertriglyceridemia and birth weight has been reported in pregnant women with and without GDM.[10–15] In a study by Schaefer-Graf et al., maternal hypertriglyceridemia has been a stronger predictor of macrosomia than glycemic control in pregnant women with GDM.[15] Maternal obesity also has an independent role in the development of macrosomia.[16] The meta-analysis conducted by Gaudet et al. revealed that maternal obesity was associated with a two-times increased risk of macrosomia.[17]

However, the role of serum triglycerides (TGs) in the development of fetal macrosomia in different subgroups of body mass index (BMI) has been neglected. In a study by Olmos et al., serum triglycerides level was not associated with birth weight in normal weight women with GDM, while the level of maternal TGs was correlated with birth weight in obese and overweight pregnant women.[12] With regards to the role of ethnicity in lipid profile status in pregnant women[18] and limited studies on BMI categories, the aim of this study was to determine the association between maternal hypertriglyceridemia and fetal macrosomia in Iranian pregnant women of different BMI subgroups with GDM.

## 2. Methods

This cohort study was conducted on 319 pregnant women with GDM referred for glucose control to Kowsar hospital in Qazvin, Iran, from January 2015 to March 2016. The study protocol was approved by the Ethics Committee of Qazvin University of Medical Sciences. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all participants gave their written informed consent forms.

The inclusion criteria were being 16–40 years old, singleton pregnancy, gestational age of 24–28 weeks, and positive 75 g oral glucose tolerance test results (fasting blood glucose $\geq$92 mg/dL and/or 1 h blood glucose $\geq$180 mg/L or/and 2 h blood glucose $\geq$153 mg/dL). The exclusion criteria were chronic renal, thyroid, or liver disease; rheumatologic diseases, e.g. SLE and antiphospholipid syndrome; a history of anticonvulsive drugs and opium use; smoking; and congenital fetal anomalies in ultrasonography. Pregnant women with hypertension and pre-eclampsia were also excluded from the study.

BMI was calculated using the self-reported height and weight of the pre-pregnancy period. A BMI less than 25 was considered normal. Obesity was defined as BMI $\geq$ 30 and overweight was defined as 25 $\leq$ BMI $<$ 30. Gestational age was determined using previous pregnancy ultrasound results. Excessive weight gain was defined as a weight gain of more than 16 kg during pregnancy.[19]

At 24th–28th weeks of pregnancy, serum level of TGs was measured after a 12 h overnight fasting using the enzymatic colorimetric method and reagent (Pars Azmoon Co, Iran). Inter-assay and intra-assay coefficients of variation were 1.6% and 1.47%, respectively. In the last weeks of pregnancy, fasting blood glucose and 2 hr postprandial glucose were recorded over phone calls. Birth weight was recorded according to the registered birth documents. A birth weight $\geq$ 4000 g was considered as macrosomia.[20]

### 2.1. Statistical analysis

Data were described as mean $\pm$ SD or frequency where appropriate. Parameters related to macrosomia were compared among BMI subgroups using ANOVA with Tukey's pot-hoc test. Logistic regression analysis was used to determine the risk of macrosomia per 1-SD increase in the level of TGs as the predictor variable, and two models were applied for adjustment. In the first model, significant variables in the univariate analysis unrelated to diabetes (gestational age at delivery and maternal age $>$ 35 years) were considered as the covariate. In the second model, variables related to diabetes (insulin use, fasting blood glucose at diagnosis, mean fasting blood glucose, and 2 hr postprandial glucose in the last weeks of pregnancy) were considered as the covariate in addition to the first-model variables. To facilitate the comparison with Olmos et al.'s study,[12] similar criteria were applied to define hypertriglyceridemia using the normal values of TGs in the pregnancy period published by Alvarez et al.[21] The 90th

percentile of the level of TGs in the third trimester of pregnancy was calculated as mean + 1.28 SD based on Alvarez et al.'s study and considered as the optimal cut-point to determine hypertriglyceridemia. Therefore, the 90th percentile of the level of TGs in the third trimester of pregnancy was 273 mg/dL.

The Receiver operating characteristic (ROC) curve of the level of TGs for the diagnosis of fetal macrosomia was depicted in the BMI subgroups separately and the area under the curve (AUC) was calculated. The optimal cut-point of the level of TGs to predict fetal macrosomia was assessed by maximum Youden index [sensitivity − (1-specificity)] on the ROC curve. P-values $< 0.05$ were considered as statistically significant.

## 3. Results

Of 319 pregnant women with GDM, 63 normal weight, 183 overweight, and 59 obese pregnant women completed the study. Fasting and postprandial blood glucose levels in the last weeks of pregnancy were available for 229 pregnant women. The baseline characteristics of lost subjects (age, TGs, fasting blood glucose, and insulin use) were not significantly different from those of other subjects. The results of birth weight in 14 pregnant women were lost due to delivery in other cities.

The clinical and biochemical characteristics of the study subjects are shown in Table 1. Gestational age at delivery significantly differed across the three groups. The longest and shortest gestational age was found in the normal weight group and obese group, respectively. The frequency of maternal age $> 35$ years was significantly higher in the overweight group compared to the other groups ($P = 0.011$). Mean weight gain and frequency of excessive weight gain during pregnancy were not significantly different among the three groups. Mean level of TGs, fasting blood glucose at GDM diagnosis, fasting and postprandial blood glucose in the last weeks of pregnancy, and prevalence of hypertriglyceridemia and insulin treatment were not different between the three BMI subgroups. After delivery, macrosomia was more prevalent in obese women compared to the other groups (32.2% vs. 19.1% in overweight women and 11.1% in normal weight women, $P < 0.05$).

The results of logistic regression analysis of the relationship between a 1-SD increase in the level of TGs as the independent factor and fetal macrosomia as the dependent factor are demonstrated in Table 2. In the univariate analysis, a 1-SD increase in the level of TGs was only associated with the increased risk of macrosomia in normal weight and overweight pregnant women. In Model 1 (adjusted for gestational age at delivery and maternal age $> 35$ years), a 1-SD increase in the level of TGs was associated with 3.4 times ($P < 0.05$) and 1.9 times ($P < 0.01$) increased risks of macrosomia in normal weight and overweight women, respectively. In the normal weight group, serum level of TGs remained an independent risk factor of macrosomia after adjusting for insulin use, fasting blood glucose at diagnosis, mean fasting blood glucose, and 2 hr postprandial glucose in the last weeks of pregnancy. Nevertheless, serum level of TGs was not associated with macrosomia in any models applied for obese women.

The AUC of the level of TGs for macrosomia was 0.828 (95% CI: 0.712−0.911, $P < 0.001$) in normal weight women, 0.711 (95% CI: 0.639−0.775, $P < 0.001$) in overweight women, and 0.549 (95% CI: 0.414−0.679, $P = 0.53$) in obese

**Table 1** Clinical and biochemical characteristics of the study subject.

| Variable | Normal weight(n = 63) | Overweight(n = 183) | Obese(n = 59) | P-value |
|---|---|---|---|---|
| Maternal | | | | |
| Age (yr)[a] | 30.4 ± 5.3 | 30.7 ± 4.0 | 31.7 ± 4.3 | 0.231 |
| Age >35 years (%) | 23.8% | 11.5% | 25.4% | 0.011* |
| Gestational age at delivery (weeks)[a] | 38.6 ± 0.9 | 38.2 ± 1.2 | 37.8 ± 1.1 | 0.001** |
| Body Mass Index (Kg/m$^2$)[a] | 23.5 ± 1.4 | 27.5 ± 1.2 | 32.5 ± 2.7 | <0.001** |
| Weight gain (Kg) | 14.1 ± 2.2 | 13.8 ± 2.4 | 13.7 ± 2.8 | 0.767 |
| Excessive weight gain (%)[b] | 13.7% | 11% | 12.5% | 0.860 |
| Triglycerides (mg/dL)[a] | 270.3 ± 65.3 | 278.2 ± 67.3 | 298.5 ± 89.6 | 0.08 |
| Hypertriglyceridemia (%)[c] | 44.4% | 51.4% | 55.9% | 0.435 |
| FBS (mg/dL)[a] | 106.6 ± 10.5 | 109.9 ± 12.7 | 109.2 ± 12.2 | 0.127 |
| Third trimester FBS (mg/dL)[a] | 96.6 ± 9.5 | 97.2 ± 8.5 | 99.6 ± 10.2 | 0.266 |
| Third trimester BS 2hpp (mg/dL)[a] | 119.4 ± 13.7 | 118.3 ± 11.6 | 119.0 ± 13.5 | 0.866 |
| Insulin treatment (%) | 46.8% | 48.3% | 46.2% | 0.688 |
| Neonatal | | | | |
| Birth weight (g)[a] | 3313.7 ± 410.3 | 3475.6 ± 512.3 | 3538.1 ± 626.8 | 0.04*** |
| Fetal macrosomia (%) | 11.1% | 19.1% | 32.2% | 0.013**** |

FBS: Fasting blood glucose; BS: Blood glucose.
* Significant difference between overweight group and normal and obese groups.
** Significant difference among the three groups.
*** Significant difference between normal weight group and overweight and obese groups.
**** Significant difference between obese groups and normal weight and overweight groups.
[a] Data are presented as mean ± SD.
[b] Weight gain > 16 kg during pregnancy.
[c] Hypertriglyceridemia was defined based on the 90th percentile of normal values in the third trimester of pregnancy in Alvarez et al.'s study (21).

**Table 2** Logistic regression analysis of the relationship between 1-SD increase in the level of TGs as the independent factor and fetal macrosomia as the dependent factor.

| Group | Crude OR | Model 1 | Model 2 |
|---|---|---|---|
| Normal weight | 4.2 (1.5−12.1)** | 3.4 (1.1−10.6)* | 16.7 (1.2−130.9.)* |
| Overweight | 1.9 (1.3−2.9)** | 1.9 (1.3−2.8)** | 1.5 (0.9−2.5) |
| Obese | 1 (0.6−1.6) | 0.9 (0.6−1.5) | 0.9 (0.5−1.9) |

Model 1: Adjusted for gestational age at delivery and maternal age >35 years.
Model 2: Adjusted for Model 1 variables + insulin use, FBS at diagnosis, mean FBS in the third trimester, and mean BS 2hpp in the third trimester.
*P < 0.05, **P < 0.01.

women. The optimal cut-off of TGs for macrosomia was 300 mg/dL in normal weight women (sensitivity: 85.7%, specificity: 73.2%) and 282 mg/dL in overweight women (sensitivity: 77.1%, specificity: 62.8%).

## 4. Discussion

In the present study, the incidence of fetal macrosomia was about three times and two times higher in obese women than normal weight and overweight women, respectively. A 1-SD increase in the level of maternal TGs at the beginning of the third trimester of pregnancy was associated with a four-times increased risk of macrosomia in normal weight women and with 1.5-times increased risk of macrosomia in overweight women. The level of TGs had an independent association with macrosomia after adjustment for known risk factors of macrosomia. In normal weight women, serum TGs greater than 300 mg/dL could predict macrosomia with 85.7% sensitivity and 73.2% specificity. The level of TGs was not associated with macrosomia in obese women.

In previous studies, the level of maternal TGs had an independent and strong association with birth weight in pregnant women with and without GDM.[10–15] There are some pathophysiological reasons for the increased risk of macrosomia in pregnant women with hypertriglyceridemia. Serum level of TGs is subject to significant changes in pregnancy trimesters. In the first trimester of pregnancy, insulin sensitivity and lipoprotein lipase activity increase. The lipoprotein lipase activity decreases in the third trimester of pregnancy due to the increase in insulin resistance, a phenomenon which is more prominent in GDM. Maternal lipoproteins will not cross the placenta but are hydrolyzed by placental lipoprotein lipase. The derived fatty acids enter the umbilical cord blood, are stored in fetal adipose tissues, and result in increased fetal growth and adiposity.[22]

There are limited reports on the association of the level of TGs in pregnant women and macrosomia in BMI subgroups. In a study by Olmos et al., z-scores of TGs had a significant correlation with birth weight z-scores in overweight and obese pregnant women ($r = 0.42$ and $r = 0.47$, $P < 0.001$, respectively), while there was no such correlation in normal weight women.[12] These results are considerably different from the results of the present study. In Olmos et al.'s study, the level of TGs and prevalence of hypertriglyceridemia was significantly lower in lean women than overweight and obese women. Nevertheless, these values did not differ across normal weight and overweight or obese women in the present study. Mean level of TGs in normal weight women was 229 ± 67.3 mg/dL in Olmos et al.'s study that is lower than the value reported in the present study. Based on the 90th percentile of Alvarez et al.'s study, the prevalence of hypertriglyceridemia was 44.4% in the present study compared to 34% in Olmos et al.'s study.[12] The lower prevalence of hypertriglyceridemia in normal weight women in Olmos et al.'s study can explain the insignificant correlation between the level of TGs and macrosomia due to the lower power in this BMI subgroup.

Differences in the serum level of TGs in normal weight women between Olmos et al.'s[12] study and the present study may be due to the differences in ethnicity and lifestyle. In another study conducted in Qazvin, the prevalence of insulin resistance in normal weight women was very high (about 40%) and hypertriglyceridemia was the strongest predictor of normal weight metabolic obesity in women.[23]

In the present study, the incidence of macrosomia in obese women was high (30%), approximately three times more than that of normal weight women. Gestational age at delivery was significantly different among the three groups, and the frequency of maternal older age was significantly lower in the overweight group. However, the association between hypertriglyceridemia and macrosomia was still not significant in obese women after adjustment for variables unrelated to diabetes in Model 1 and other variables related to blood glucose control in Model 2. The reason for this finding and the difference with Olmos et al.'s study[12] is unclear. Considering the high incidence rate of macrosomia in obese women in the present study, it seems that other stronger factors may be involved in the development of macrosomia in obese pregnant women with GDM.

In the present study, despite the significant difference in the incidence of macrosomia among the three groups, blood glucose at GDM diagnosis and insulin therapy rate were not different among the groups. Blood glucose in the last weeks of pregnancy was missed in 25% of study participants. It can be suggested that the glycemic control in the obese group has probably been worse than the non-obese group. However, mean blood glucose at GDM diagnosis and insulin therapy rate were not different between participants with missed blood glucose in the last weeks of pregnancy compared with other participants. Therefore, there is no evidence for a worse glycemic control in obese women with missed blood glucose in the last weeks of pregnancy.

In addition to lipids and glucose, amino acids, glycerol, and keton bodies play a role in fetal growth.[24] In Aye et al.'s study, an increase in placental p33-mitogen-activated protein kinase (MAPK) phosphorylation was found in obese women, a phenomenon which correlated with fetal growth. They hypothesized that increased inflammatory mediators in obese pregnant women induce an increase in MAPK phosphorylation that leads to an increase in the transfer of nutrients (e.g. amino acids) to the placenta and development of macrosomia.[25]

In a study by Aye et al.[26] on mice, an increase in insulin and decrease in peroxisome proliferator-activated receptor-α (PPARα) phosphorylation in the placenta was associated with an increase in the transfer of amino acids and glucose and a 29% increase in fetal weight. The mentioned changes and fetal weight were returned to normal after the administration of adiponectin to mothers. Therefore, a decrease in adiponectin in obese women can play a role in fetal macrosomia.

There are reports that placental lipoprotein lipase increases, inflammatory cells (e.g. macrophages and neutrophils) accumulate, and the expression of inflammatory inhibitors (e.g. TNF-α, IL-1, and IL-6) increases in the placenta of obese women.[27] The effect of IL-6 on the accumulation of fatty acids has also been reported in cultured human trophoblast.[28] In addition, vascular changes in the placenta of obese women can potentially increase the transfer of nutrients through the placenta.[29] With regards to the noted studies, the high prevalence of macrosomia in obese women is multifactorial and cannot be attributed to a single factor such as hypertriglyceridemia.

In the present study, the optimal cut-point of TGs was 300 mg/dL in normal weight women and 287 mg/dL in overweight women. In Son et al.'s study[11] on pregnant women with GDM, the optimal cut-point of TGs (294 mg/dL) was similar to that of the present study with 48% sensitivity and 83.5% specificity, but sensitivity and specificity were not evaluated in BMI subgroups.

The main limitation of the present study was the missed blood glucose in the last weeks of pregnancy in 25% of the participants. Nevertheless, mean fasting blood glucose in the second trimester of pregnancy and frequency of insulin therapy in this group were not different from those of other participants. BMI classification was based on pre-pregnancy values self-reported by pregnant women. Still, the accuracy of self-reported BMI for evaluating diseases and their complications was appropriate in the study by McAdams et al.[30] The strength of the present study was studying a population with special metabolic disturbances including high insulin resistance in the normal weight population and the new finding of lack of association between the level of maternal TGs and macrosomia in obese subjects.

In summary, the prevalence of hypertriglyceridemia did not significantly differ among normal weight and obese or overweight women with GDM. Although hypertriglyceridemia was a strong predictor of macrosomia in normal weight women, its association with macrosomia was weak in overweight women. There was no association between hypertriglyceridemia and macrosomia in obese women. With regards to the difference between the results of the present study and those of previous studies, more studies on various ethnicities and lifestyles are necessary.

## Conflict of interest

Nothing to declare.

## Acknowledgments

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## Appendix A. Supplementary data

Supplementary data related to this chapter can be found at https://doi.org/10.1016/j.pedneo.2018.01.008.