MATERNAL TRIGLYCERIDES LEVELS AND NEWBORN WEIGHT IN PREGNANT DIABETIC WOMEN

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ABSTRACT
The research aimed to determine the predictive value of serum triglyceride levels (TG) for neonatal weight in pregnant women with positive diabetic screening but normal glucose tolerance. Pre-pregnancy 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 positive screening test. TG levels measured in the third trimester of pregnancy are independent of the genetic polymorphism of ApoE.

KEYWORDS: Maternal Triglycerides, Newborn.

INTRODUCTION
Fetal growth is affected by genetic, demographic and metabolic factors of the mother[1]. In particular, disturbances of maternal glucose metabolism are known to favour fetal overgrowth and macrosomia, a major complication of gestational diabetes mellitus (GDM).[1]

The relationship between plasma glucose levels and fetal growth seems to be linear, as an increased incidence of macrosomia and large for gestational age (LGA) newborns have been recorded even in women with abnormal diabetic screening but normal glucose tolerance test.[1] Alternatively, nutritional/metabolic factors other than glucose might contribute to excessive fetal growth in the presence of non-diagnostic alterations of maternal glucose. Serum lipid levels provide an attractive alternative. Lipid metabolism changes significantly during physiologic pregnancy[2] and genetic factors, such as the polymorphism of the ApoE gene could potentially influence lipid metabolism in normal pregnancy.[3] In addition, an association between maternal serum triglycerides (TG) and the newborn’s body weight have recently been reported. However, in one case, non-fasting TG was determined, while in the other one the only woman with positive diabetic screening was evaluated.[4]
Fetal birth weight (BW) is an important predictive parameter for both neonatal and maternal morbidity and mortality. Therefore, accurate prediction of BW may be an invaluable tool for determining further obstetric management.[5]

In addition, prevention of BW abnormalities would prevent the long-term consequences of the offspring.[6] Fetal growth and development are affected by genetic, demographic and metabolic factors of the mother.[7] In particular, disturbances of maternal glucose metabolism are known to favor fetal overgrowth and macrosomia, a major complication of gestational diabetes mellitus (GDM).[8] The relation between plasma glucose levels and fetal growth seems to be linear[9] as an increased incidence of fetal macrosomia and large for gestational age (LGA) newborns have been reported in all types of diabetic pregnancy, especially in a woman with poor glycemic control.[10] Moreover, macrosomia has been recorded even in women with abnormal glucose screening but normal glucose tolerance test.[11] In spite of this strong relation between macrosomia and presence of diabetes mellitus (DM) in pregnant women, fetal macrosomia may occur despite maternal euglycemia[12] and strict glycemic control sometimes failed to prevent macrosomia.[13]

Alternatively, nutritional and metabolic factors other than glucose might contribute to excessive fetal growth. Serum lipid levels that show significant physiological changes during pregnancy may provide such an attractive alternative.[14] The physiological maternal hyperlipidemia during pregnancy especially in mid to late gestation is believed to be beneficial to the mother and fetus in terms of lactation and nutrition.[15]

Although there are accumulating data showing that maternal serum triglycerides (TG) level all over pregnancy, whether fasting or randomly sampled are significantly and independently positively associated with BW at term, the role of this maternal hyperlipidemia in fetal growth regulation and its effect on BW is not yet well established.[16]

Brown et al. in studies of American women without chronic diseases described that 1-kg weight gain in the first trimester predicted a 31-g increase in newborn weight, and 1-kg weight gain in the second trimester predicted a 26-g increase in newborn weight. However, it was noted that in women who lost weight during the first trimester, their fetus's birth weight was 211 g lower. In studies performed among healthy Brazilian pregnant women, it was found that the pregnancy weight gain, monitored during the gestational trimesters, influenced birth weight positively.[17]
Each kilogram gained during the first, second and third trimester corresponded to 30 g (β=29.6; p=0.040), 27 g (β=27.2; p=0.045) and 43 g (β=42.6; p=0.001), respectively, in birth weight.\[18\]

There is increasing evidence that maternal metabolism and intrauterine conditions affect the development and growth of children, with consequences for their health later in life, called the fetal origins hypothesis.\[1-3\] One of these prenatal metabolic factors could be the maternal lipid profile, including levels of triglycerides (TG) and total cholesterol (TC).

Both TG and TC are essential factors for optimal development of the fetus, and these 2 lipids are known to be taken up by the placenta and metabolized and transported in various forms to the fetus.\[19\] When pregnancy progresses, lipid levels increase, which suggests the necessity of these metabolic changes for pregnancy maintenance and fetal growth.\[4\] Indeed, low maternal TG and TC, levels during pregnancy are related to delayed prenatal growth and an increased risk of the infant to be born small for gestational age (SGA).\[20\] SGA may have serious health consequences later in life, such as a higher risk for premature cardiometabolic diseases, for example, coronary heart disease, type 2 diabetes, and hypertension.\[21\]

In addition to prenatal growth, postnatal growth also may predict the development of disease later in life.\[22\] The majority of infants who are born SGA show an accelerated postnatal growth and rapid weight gain.\[23\]

This rapid weight gain contributes to improved immunity, with a positive effect on childhood survival.\[24\] However, it also is related to negative effects on health in the long term, such as obesity and cardiovascular diseases in adulthood.\[25\]

Overweight and obesity, which are associated with elevated maternal TG and TC levels during pregnancy, are increasing in the Western world. Increased maternal TG and TC levels may be associated with infants who are born large for gestational age (LGA). Infants with LGA have an increased risk of obesity and metabolic disorders later in life.\[2,14\] Thus, both high and low levels of maternal TG and TC may have negative consequences for pre- and postnatal growth.\[26\]

So far, most studies about pregnancy outcomes used TC and/or TG levels during the third trimester of pregnancy. It is less clear whether TC and/or TG levels during the first trimester
of pregnancy are associated with birth weight (BW). Moreover, the association with postnatal accelerated growth has not been elucidated.

BACKGROUND
Fetal macrosomia is one of the major complications of diabetic pregnancy. According to Pedersen’s hypothesis,[1] fetal macrosomia is associated with fetal hyperglycemia and related hyperinsulinemia resulting from maternal hyperglycemia. Although diabetic mothers with poor glycemic control during pregnancy were more likely to deliver macrosomic infants compared with those who had good glycemic control,[2,3] strict glycemic control sometimes failed to prevent macrosomia. It was reported that the risk of having a large for gestational age (LGA) infant was reduced if intensive glycemic control was begun before but not after 32 weeks’ gestation.[4] Those reports suggested that diabetic macrosomia is associated with the maternal metabolic condition at a certain gestational age. Conversely, even a minor degree of maternal glucose intolerance also represents an increased risk of macrosomia.[5] A significantly higher incidence of LGA infants was observed in women with abnormal diabetic screening but normal oral glucose tolerance test (GTT) in comparison with those who had negative diabetic screens.[6,7] These findings suggest fetal growth is determined largely by maternal factors, including not only plasma glucose levels but also other fuels, such as lipids and amino acids,[8] especially in nondiabetic women. Maternal serum lipid levels increase during mid to late gestation, which is believed to be beneficial to mother and fetus in terms of lactation and nutrition.[9] A recent study reported that postprandial triglyceride but not postprandial glucose levels at diabetic screen at 24–28 weeks’ gestation were significantly associated with relative birth weight (the observed birth weight/the 50th percentile birth weight for gestational age).[27] However, it has not been documented conclusively whether elevated triglyceride levels are associated with the risk of fetal macrosomia. Furthermore, it is not known whether midpregnancy maternal fasting triglyceride levels are associated with birth weight, independent of maternal glucose levels and obesity.

We studied nondiabetic women with the positive midpregnancy diabetic screen, a group at high risk of fetal macrosomia. Our objective was to determine whether maternal serum lipid levels, including triglyceride, free fatty acids, and total cholesterol, at 24–32 weeks’ gestation is associated with newborn weight at term, and therefore, associated with a risk of developing an LGA infant and whether the association is independent of maternal obesity and plasma glucose levels.[28]
METHODS
This study involved 180 pregnant Iraqi women with positive diabetic screening performed at 24 to 30th week of gestation. The GCT consisted of a standard 50-g glucose load performed after an overnight fast and a 1-h plasma glucose concentration was measured. A plasma glucose value of ≥ 7.8 mmol/l was considered positive according to these recommendations.[29]

All women with positive GCT performed a 3-h 100-g oral glucose tolerance test (OGTT). After an overnight fast, blood was taken to determine plasma glucose levels, serum lipid concentration and DNA analysis. According to Carpenter and Coustan’s criteria the cut-off values were the following:

fasting glycaemia: 5.3 mmol/l, 1 h: 10.0 mmol/l, 2 h: 8.6 mmol/l, 3 h: 7.8 mmol/l. Two or more of the cut-off values must be met or exceeded for a diagnosis of gestational diabetes mellitus (GDM); women with one altered value were classified as impaired glucose tolerant (IGT). Women who did not meet the cut-off value were considered normotolerant (NGT).

Anamnestic, clinical, and anthropometric parameters (including pre-pregnancy body mass index) were recorded.

The gestational age was estimated by last menstrual period, confirmed or corrected by ultrasonography. All subjects were followed until delivery. Information regarding time and mode of delivery, birth weight and neonatal morbidity were obtained in all women.

The study protocol was approved by the local Ethical Committee and all women gave their voluntary informed consent before entering the study.

Deliveries were defined as pre-term when they occurred before the 37th week of gestation. Macrosomia was diagnosed for neonatal body weight ≥ 4 kg or as a neonatal weight greater than the 90th percentile for gestational age (LGA).[30]

Plasma glucose concentration was determined by the glucose-oxidase method on a Beckman Glucose Analyser II. The inter- and intra-assay coefficient of variation was < 3%.
Triglycerides, total, LDL- and HDL-cholesterol concentrations were determined by using standard enzymatic procedures on an automatic analyser (Modular—Roche Diagnostics, Germany). The inter- and intra-assay coefficient of variation for all parameters was < 5%.

DNA was extracted from peripheral leucocytes using a standard protocol. The ApoE genotype of each extracted DNA sample was determined by polymerase chain reaction (PCR) and restriction endonuclease CfoI, followed by polyacrylamide gel electrophoresis of the amplified products.

RESULTS

OGTT results by OGTT, performed at an average gestational age of 27 ± 3.7 weeks, we identified GDM in 36 women (20%), IGT in 23 (13%) and NGT in 121 (67%). Lipid profile Mean total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, TG levels in different classes of glucose tolerance. Serum TG concentration was significantly higher (P < 0.01) in women with GDM as compared with NGT or IGT, while total, LDL- and HDL-cholesterol did not differ among the three groups. ApoE polymorphism ApoE polymorphism was determined in all women resulting in an ApoE3 allelic frequency of 86%, whereas the allelic frequency for ApoE2 and ApoE4 were 5% and 9%, respectively. As expected, ApoE3E3 genotype showed the highest frequency (73%). As reported in Table 3, we found no clear-cut association between apoE genotype and serum TG concentration.

Pregnancy outcome the mean time of delivery was 39.3 weeks (interquartile range 39–40) with a 31% rate of caesarean section. Average neonatal body weight was 3442 ± 440 g. Newborns from IGT mothers were heavier (3520 ± 513 g) than those from NGT (3442 ± 403 g), and GDM (3253 ± 508 g). Accordingly, the prevalence of macrosomia and LGA newborns was higher in IGT than in GDM and NGT group (macrosomia: 21.8% vs. 10 and 6.18%; LGA: 20% vs. 17.4 and 15.6%, respectively, all P < 0.01). Newborn weight in GDM women who delivered at term was significantly correlated to fasting plasma glucose during OGTT (r² = 0.24; P = 0.04) and pre-pregnancy BMI (r² = 0.23; P = 0.04); in IGT mothers no correlation was found between newborn weight and other variables considered. In 83 NGT women who delivered at term, the influence of lipid parameters on newborn weight was evaluated. The prevalence of LGA infants was significantly higher (P < 0.05) in women with hypertriglyceridaemia (TG levels > 75th percentile value; 2.30 mmol/l) than in those with normal TG levels (4 of 19, 21% and 2 of 44, 4.5%, respectively).
DISCUSSION

Fetal metabolism and fetal growth are dependent on nutrients crossing the placenta. Therefore, the mother's metabolism undergoes changes that allow a continuous supply of glucose and amino acids, whereas FFA and glycerol cross the placenta barrier to a lesser extent.\[32\]

An excess of glucose supply, as occurs in the case of diabetic mothers, will cause fetal hyperinsulinaemia which, in turn, will favour macrosomia.

Moreover, an increase in glucose levels below the diagnostic threshold for diabetes in the second half of pregnancy is associated with a continuous increase in macrosomia. An increased incidence of LGA infants and macrosomia in women with abnormal screening for GDM but normal glucose tolerance test has been previously described. In this group, the rate of macrosomia is two-to-three times higher than in women with a normal diabetic screening test.\[33\] Moreover, it has been demonstrated that dietary counselling and home blood glucose monitoring significantly reduce the incidence of macrosomia.\[34\] Other metabolic disturbances may also contribute to fetal overgrowth. Lipid metabolism also alters during pregnancy,\[35\] and serum TG concentration may predict neonatal body weight.\[36\]

However, most data are limited to women with altered glucose tolerance. For this reason, we studied the effect of lipid metabolism on fetal growth in women with positive screening but normal glucose tolerance. In this group, only pre-pregnancy BMI and serum fasting TG determined in the third trimester had an independent role in the multivariate analysis. The association between pre-pregnancy BMI and birth weight has been confirmed in previous studies in women with GDM as well as those with normal tolerance.\[37\] There is little information on the effects of TG levels. A positive correlation between non-fasting serum TG and birth weight was reported in GDM women independent of maternal BMI and rate of weight gain.\[38\] Moreover, in GDM, insulin therapy reduces both the incidence of macrosomia and post-meal triglyceride levels.\[39\] A relationship between fasting serum TG and newborn body weight has been reported in pregnant Japanese women with normal 75-g OGTT (but positive screening test) at 24th to 32nd weeks of gestation.\[40\] We now provide evidence that also in Caucasian normotolerant women with positive diabetic screening, fasting TG concentration is positively correlated with at term newborn weight irrespective of plasma glucose levels and body weight. These data suggest that elevated maternal TG contributes to macrosomia irrespective of glucose tolerance. An increase in the TG occurs
during late gestation due to enhanced hepatic production of VLDL triglycerides under the effect of high oestrogen.\[41\] There is also an increase in intestinal absorption of dietary lipid and reduced clearance of TG due to decreased extrahepatic lipoprotein lipase activity.\[42\]

These changes coincide with reduced insulin sensitivity which may also contribute to the increase in TG. The association with newborns’ body weight may reflect secondary

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.10-15There 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.\[43\]

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.\[44\]
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. The 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.\[45\]

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.\[46\]

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 the 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.\[47\]

REFERENCES


