OBSTETRICS

Comparison of Triglyceride Level between 24-28 week's Gestation of Nondiabetic Women with and without Positive Diabetic Screening

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ABSTRACT

Objectives: To determine the difference in triglyceride levels (TG) between normal and abnormal glucose screening test but not diagnosed GDM in pregnant women.

Materials and Methods: A prospective cohort study was conducted in 108 singleton pregnant women undergoing 50g glucose challenge test (50g GCT) at 24 to 28 weeks of gestation during June to November 2015. Eighty four in control group had normal 50g GCT and twenty four subjects with abnormal 50g GCT but negative on diagnostic test [100g oral glucose tolerance test (OGTT)] in study group. The TG and fasting blood sugar (FBS) were collected in both groups after 50g GCT for one week. Hypertriglyceridemia was defined as triglyceride level of 75th percentile or greater. The Receiver Operator Characteristic (ROC) curve was constructed to look for the cut-off level of TG which provide the best sensitivity and specificity of large for gestational age (LGA).

Results: There was no significant difference in TG which was 188 and 189 mg/dl in control and study group respectively (p = 0.402). Hypertriglyceridemia was 237 mg/dl or greater. Incidence of hypertriglyceridemia was not different between groups (p = 0.508). The percentage of LGA in the study group was 29.2% while in the control group was 9.5% (p = 0.039). Using the cut-off TG > 183.5 mg/dl has a sensitivity of 60% and specificity of 44% for LGA detection.

Conclusion: TG was not different between pregnant women with normal 50g GCT and those who had abnormal 50g GCT but negative on diagnostic test. The TG was not good indicator for LGA detection.

Keywords: triglyceride level, positive diabetic screening, large for gestational age

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เปรียบเทียบระดับไตรกลีเซอร์ไรด์ระหว่างสตรีตั้งครรภ์ที่มีผลการตรวจคัดกรองเบาหวานปกติและผิดปกติ แต่ไม่เป็นเบาหวานระหว่างตั้งครรภ์ที่อายุครรภ์ 24-28 สัปดาห์

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบความแตกต่างของระดับไตรกลีเซอร์ไรด์ระหว่างสตรีตั้งครรภ์ปกติและสตรีตั้งครรภ์ ที่ผลตรวจคัดกรองเบาหวานผิดปกติแต่ไม่เป็นเบาหวานระหว่างตั้งครรภ์

วัสดุและวิธีการ: การศึกษาแบบ prospective cohort ในสตรีตั้งครรภ์เดี่ยว 108 ราย ซึ่งได้รับการตรวจคัดกรองเบาหวาน ด้วยการกลืนน้ำตาล 50 กรัม ที่อายุครรภ์ 24 ถึง 28 สัปดาห์ ระหว่างเดือนมิถุนายน ถึง พฤศจิกายน ค.ศ.2015 แบ่งเป็นกลุ่ม ควบคุม 84 ราย ที่มีผลการตรวจคัดกรองเบาหวานปกติ และกลุ่มศึกษา 24 ราย ที่มีผลการตรวจคัดกรองเบาหวานผิดปกติแต่ ไม่เป็นเบาหวานขณะตั้งครรภ์ ด้วยการกลืนน้ำตาล 100 กรัม หลังจากการตรวจคัดกรองเบาหวานหนึ่งสัปดาห์ถัดมา สตรีตั้ง ครรภ์ทั้งสองกลุ่มจะได้รับการตรวจไตรกลีเซอร์ไรด์และระดับน้ำตาลในเลือด โดยภาวะไตรกลีเซอร์ไรด์ในเลือดสูงจำกัดความ ถึงระดับไตรกลีเซอร์ไรด์ที่มากกว่าเปอร์เซนไทล์ที่ 75 ของประชากรทั้งหมด และใช้ Receiver Operator Characteristic curv ePitจารณาหาจุดตัดของระดับไตรกลีเซอร์ไรด์ที่พบภาวะทารกตัวโต

ผลการวิจัย: ค่าเฉลี่ยระดับไตรกลีเซอร์ไรด์ของกลุ่มควบคุมคือ 188 mg/dl และกลุ่มศึกษาคือ 189 mg/dl ซึ่งพบว่าไม่มีความ แตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างสตรีตั้งครรภ์ทั้งสองกลุ่ม (p = 0.402) ภาวะไตรกลีเซอร์ไรด์ในเลือดสูงมีค่ามากกว่า 237 mg/dl ซึ่งจำนวนของสตรีตั้งครรภ์ทั้งสองกลุ่มที่มีภาวะนี้ มีจำนวนไม่แตกต่างกัน (p = 0.508) ร้อยละ 29.2 ของสตรีตั้ง ครรภ์ในกลุ่มศึกษาคลอดทารกตัวโต ในขณะที่กลุ่มควบคุมคลอดทารกตัวโตเพียงร้อยละ 9.5 ซึ่งแตกต่างกันอย่างมีนัยสำคัญ ทางสถิติ (p = 0.039) นอกจากนี้สตรีตั้งครรภ์ร้อยละ 60 ที่มีระดับไตรกลีเซอร์ไรด์มากกว่าหรือเท่ากับ 183.5 mg/dl จะสามารถ พบภาวะทารกตัวโตได้ แต่ทั้งนี้มีความจำเพาะเพียงแค่ร้อยละ 44

สรุป: สตรีตั้งครรภ์ที่มีผลการตรวจคัดกรองเบาหวานปกติและผิดปกติ จะมีระดับไตรกลีเซอร์ไรด์ที่ไม่แตกต่างกัน และระดับ ไตรกลีเซอร์ไรด์อาจจะไม่สัมพันธ์จำเพาะกับการพบภาวะทารกตัวโต

คำสำคัญ: ระดับไตรกลีเซอร์ไรด์, ผลตรวจคัดกรองเบาหวานผิดปกติ, ภาวะทารกตัวโต

Introduction

Large for gestational age (LGA) refers to neonatal birth weight (BW) greater than the 90th percentile for gestational age (GA)[1-3]. Two large studies of pregnant Chinese women reported the increasing percentage of LGA year by year from 13.72% to 18.08%[4] and 8.31 to 10.50%[5], respectively. It is commonly known that LGA has many adverse effects on mothers and newborns such as increased rate of cesarean section, postpartum hemorrhage, shoulder dystocia, fractured clavicle and brachial plexus injury[6,7]. These adverse events might occasionally be threatening. Therefore, many clinicians tried to study and reported on associated risk factors for LGA. For example; multipara, previous LGA newborn, maternal age less than 17 years, maternal weight gain more than 15 kg, maternal obesity and especially gestational diabetes mellitus (GDM) in pregnancy[6,8,9]. GDM remains a major risk factor for LGA. Other than decreasing of insulin level in normal maternal physiology, insulin resistance is a cause of GDM in pregnancy[13,14,15]. As well as ketones and glucose, fat is also essential for fetal growth. There are some well known association between increasing insulin resistance and lipolysis of peripheral adipose tissue leading to maternal hypertriglyceridemia[13]. After free fatty acid and glycerol, the metabolized form of triglyceride, change to the active form, they can then cross placenta to fetus. Therefore triglyceride can affect fetal weight and hypertriglyceridemia may be a cause of LGA newborns.

Recent studies have shown that pregnant women who had GDM or who were positive for diabetics screening test also had hypertriglyceridemia and delivered LGA newborns[14,15]. There are some studies showing association between hypertriglyceridemia and poor pregnancy outcomes such as preeclampsia, preterm birth, maternal pancreatitis and especially LGA newborns[16,17]. Although hypertriglyceridemia had many effects on maternal and neonatal outcomes, there is no standard screening test at present such as GDM screening test according to ACOG guidelines[18].

This study focuses on non-diabetic pregnant women with positive diabetic screening because they are at high risk of LGA newborns but there is a lack of data about them. Most studies[11,17] researched in GDM pregnant women. The primary objective of this study was to compare maternal fasting serum TG between normal and positive diabetic screening pregnant women but negative on diagnostic test. The secondary objective was to look for the cut-off level of TG which provide the best sensitivity and specificity of large for gestational age (LGA).

Materials and Methods

This prospective cohort study was conducted by reviewing medical records of pregnant women who presented for antenatal care and delivered in our institution during June to November 2015. Eligibility criteria were singleton pregnant women who received 50g glucose challenge test (GCT) for standard screening GDM protocol between 24 to 28 weeks of gestation. These women had to have a certain gestational age by their last menstrual period (LMP) or by early ultrasound examination at an initial visit. Exclusion criteria were women who had a medical disorder or any condition which may have affected pregnancy outcomes (e.g. pre-existing diabetes, chronic hypertension, thyroid disease, autoimmune disease, anti-phospholipid syndrome, etc). This study was approved by the Vajira Institutional Review Board (Registered Number 50/2558).

We divided the study population into two groups: study and control groups. The study subjects were pregnant women who had abnormal GCT (50g GCT ≥ 140 mg/dl) and normal 100g oral glucose tolerance test (OGTT) while the control subjects had normal GCT (50g GCT < 140 mg/dl). We collected fasting triglyceride (TG) and fasting blood sugar (FBS) in both groups after taking 50g GCT for one week. The 100g OGTT was performed in study group at the same time. Maternal hypertriglyceridemia was defined as 75thpercentile or greater of TG in all subjects[18].

We compared maternal TG between the two groups. From our pilot investigation of total 42 gravidas, the mean TG in control group was 184.66 mg/dl while the study group's was 220 mg/dl. The sample size was

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then calculated using 80% of power and 5% level of statistical significance for determining the difference between groups and the ratio between groups was 3.6:1 with unmatched design. We added 10% to the number calculated in both groups. This resulted in total of 24 study subjects and 84 controls needed. Data collection included maternal demographic, antenatal characteristics, delivery information, adverse pregnancy outcomes and neonatal birth weight. Body mass index (BMI) was calculated from self-reported pre-pregnancy weight (kg) divided by square of height (m²). Gestational weight gain during pregnancy was defined as the weight measured on the date of admission to delivery ward minus pre-pregnancy weight. LGA referred to neonatal birth weight above the 90th percentile for their gestation.

Statistical analysis was performed using SPSS software package version 22 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using student t-test or Mann-Whitney U test while categorical variables were compared by Chi-square or Fisher's exact test as appropriate. P<0.05 was considered statistically significant. ROC was constructed to find the best cut-off level of TG to obtain good sensitivity & specificity to detect LGA.

Results

A total 108 singleton pregnant women who met the inclusion criteria were enrolled. Eighty four women were in control group and twenty four gravidas were in study group. Maternal demographic and antenatal characteristics of pregnant women in the study and control groups were presented in Table 1. Both groups had similar characteristics of parity, graduation, pre-pregnancy BMI, total weight gain throughout pregnancy and GA that TG was collected. The differences between both groups were that the study group had significantly higher mean age, 50g GCT and FBS.

Table 1. Demographic and antenatal characteristics of the study population.

Characteristic	Control group (n=84)	Study group (n=24)	p value
Age (years)	25.80 ± 6.20	31.88 ± 5.72	< 0.001
Parity			0.571*
Nullipara	44 (52.4)	11 (45.8)	
Primi/Multipara	40 (47.6)	13 (54.2)	
Education			0.225*
Under bachelor degree	72 (85.7)	18 (75)	
Above bachelor degree	12 (14.3)	6 (25)	
Prepregnancy BMI (kg/m²)			0.177*
< 20.0	29 (34.5)	11 (45.8)	
20.0-24.9	5 (6.0)	4 (16.7)	
25.0-29.9	20 (23.8)	4 (16.7)	
≥ 30.0	30 (35.7)	5 (20.8)	
Total weight gain (kg)	13 (8-16)	12 (9-19)	0.559
GA for TG (weeks)	27 (26-28)	28 (27-28)	0.054
50g GCT (mg/dl)	110.61 ± 16.37	158.92 ± 12.32	< 0.001
FBS (mg/dl)	73.96 ± 7.59	78.42 ± 6.31	0.01

Data are mean ± SD, median (IQR 25-75%) or n (%)
Abbreviation: ANC = antenatal care; BMI = body mass index; GA = gestational age; TG = triglyceride; GCT = glucose challenge test; FBS = fasting blood sugar.
* Chi-Square test, ** Fisher's exact test

The TG in control group was 188 mg/dl while study group was 189 mg/dl and there was no significantly difference (p = 0.326). The hypertriglyceridemia in this study was 237 mg/dl (≥75th percentile of all TG in second trimester). Pregnant women who had hypertrigliceridemia in both groups were not different (p = 0.508). These results were shown in Table 2.

With respect to delivery outcomes, there were no significance differences of GA at delivery, gender, neonatal birth weight and route of delivery. The study group had significantly more LGA newborn than the control group (p = 0.039) which was presented in Table 3. Indications of cesarean section in both groups were previous cesarean section and other indication were cephalopelvic disproportion (CPD) and non-reassuring fetal heart rate. The indication for vacuum extraction in control group was maternal exhaustion.

Table 2. Triglyceride data of study population.

Triglyceride	Control group (n=84)	Study group (n=24)	p value
Triglyceride (mg/dl)	188 (146.25-230.50)	189 (169.50-241.75)	0.326
Hypertriglyceridemia# (237 mg/dl)	19 (22.6)	7 (29.2)	0.508*

Data are median (IQR 25-75%) or n (%)
*Chi-Square test
#Hypertriglyceridemia defined as value more than the 75th percentile of TG in all subjects[18] (TG ≥ 237 mg/dl)

Table 3. Delivery outcomes of study population.

Delivery outcome	Control group (n=84)	Study group (n=24)	p value
GA at birth (weeks)	39 (38-39)	38 (38-39)	0.194
Gender	19 (22.6)	7 (29.2)	0.508*
Male			
Female			
Birth weight (g)	3063.29 ± 366.14	3218.08 ± 485.94	0.094
LGA	8 (9.5)	7 (29.2)	0.039*
Route of delivery			
Vaginal delivery			0.701*
Spontaneous delivery	55 (65.5)	17 (70.8)	
Vacuum extraction	1 (1.2)	0	
Cesarean section	28 (33.3)	7(29.2)	

Data are mean ± SD, median (IQR 25-75%) or n (%)
Abbreviation: GA = gestational age; LGA = large for gestational age; n = number; SD = standard deviation
*Chi-Square test, **Fisher's exact test

The threshold of TG associated with LGA was analyzed by ROC curve as shown as Fig. 1. We found that 183.5 mg/dl or greater of TG was associated with LGA with 60% sensitivity and 44% specificity. Further analysis revealed the association between 50g GCT, FBS and especially BS (combination of 50g GCT and FBS) with LGA. The 50g GCT at value 134.5 mg/dl or greater yielded a sensitivity of 60% with specificity of 78%. The optimal cut off FBS ≥ 76.5 mg/dl had 67% sensitivity and 69% specificity.

In addition, BS ≥ 204.5 mg/dl yielded a sensitivity of 73.3% with specificity of 72% with LR for positive test of 2.62, PPV of 30% and NPV of 94% as shown in Table 4.
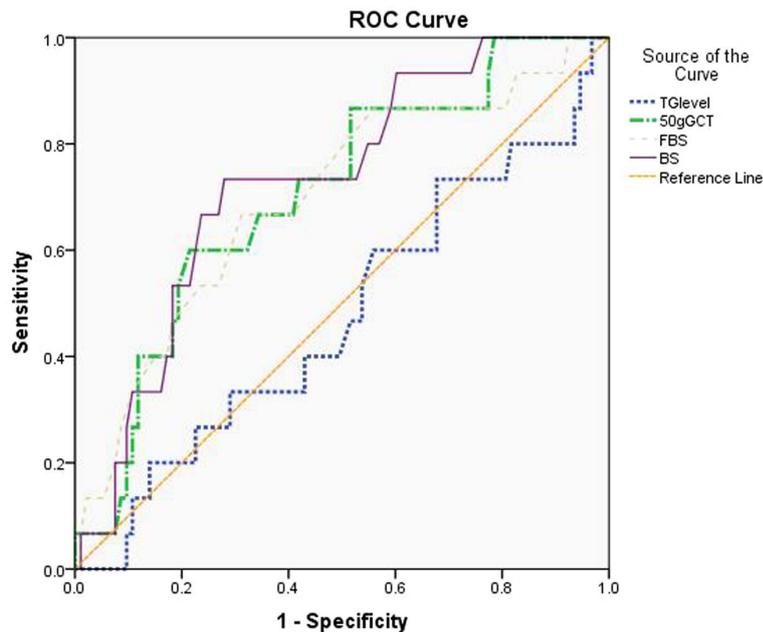

Fig. 1. The association of TG, 50g GCT, FBS and BS with LGA

Table 4. The optimal threshold associated with LGA.

	Sensitivity (95% CI)	Study group (n=24)	LR+ (95% CI)	LR- (95% CI)	PPV (95% CI)	NPV (95% CI)
TG ≥ 183.5 mg/dl	60 (0.08-0.22)	44 (0.30-0.55)	1.07 (0.68-1.68)	0.9 (0.47-1.73)	15 (0.07-0.27)	87 (0.73-0.95)
50g GCT ≥ 134.5 mg/dl	60 (0.33-0.82)	78 (0.68-0.86)	2.79 (1.58-4.92)	0.51 (0.03-0.16)	31 (0.16-0.51)	92 (0.84-0.97)
FBS ≥ 76.5 mg/dl	67 (0.39-0.87)	69 (0.58-0.78)	2.13 (1.34-3.41)	0.48 (0.23-1.00)	26 (0.14-0.42)	93 (0.83-0.97)
BS ≥ 204.5 mg/dl	73 (0.45-0.91)	72 (0.62-0.81)	2.62 (1.68-4.1)	0.37 (0.16-0.86)	30 (0.16-0.47)	94 (0.85-0.98)

Abbreviation: TG = triglyceride; GCT = glucose challenge test; FBS = fasting blood sugar; BS = blood sugar; LGA = large for gestational age; CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value

Discussion

Many studies have reported that maternal GDM showed a significant raising TG than non GDM mothers[11,19,20]. But currently, there is a lack of data to compare triglyceride level in nondiabetic with and without positive GDM screening. Our study presented

the median of TG in control and study group are 188 and 189 mg/dl. There was no significant difference between groups. That because in GDM women, there were more increasing of insulin resistance than nondiabetic with or without positive screening. Increased insulin resistance and estrogen stimulation during pregnancy are responsible for maternal hypertriglyceridemia.

Furthermore, previous study has shown that non GDM pregnant women who had positive for diabetes screening test gave birth LGA when TG ≥ 259 mg/dl (OR 11.6; 95%CI 1.1, 1.22)[18]. The incidence of LGA is 21% in hypertriglyceridemia mothers (TG > 203.71 mg/dl) while but only 4.5% among the mothers with normal TG[21]. Contrast to our study, there were no significant difference in incidence of LGA between hypertriglyceridemia and non hypertriglyceridemia pregnant women (15% versus 13.4%, p = 0.75) when using cut-off of hypertriglyceridemia > 237 mg/dl. And there were no correlation between hypertriglyceridemia and LGA while using Fisher's exact test (p = 0.754). This might be due to there were many difference factors in our study: younger maternal age than previous studies[18]; diet[22]; and ethnicity[23]. These factors may affect TG. Because of contradictory results between this study and previous studies, larger sample size is needed for future study.

Leikin et al found that the incidence of fetal macrosomia was significantly higher in non-diabetes women with abnormal 50g GCT (serum glucose ≥135 mg/dl) than women with normal 50g GCT (p = 0.0086)[24]. Likewise, we were able to find that the higher blood sugar whether the 50g GCT or FBS especially BS were more highly sensitivity and specificity to detected LGA. The strength of this study was the prospective cohort; maternal demographic and clinical data were completed. Our study only included uncomplicated pregnancy so potential influence in result of maternal blood could be excluded. However, our research was conducted in small population and focused mainly on the TG for comparing between groups so could not determine the association of TG and LGA. This limitation may be reduced in the further study with larger sample size.

Conclusion

Tthe TG showed no different between pregnant women with normal 50g GCT and those who had abnormal 50g GCT but negative on diagnostic test. There were no association between TG and LGA while maternal BS remained a major factor for LGA detection in our study.

Potential conflicts of interest

The authors declare no conflict of interest.

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