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First Trimester Neck Circumference As a Predictor For the Development of Gestational Diabetes Mellitus

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Short title: Neck Circumference predicting Gestational Diabetes Mellitus

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Abstract

Backgrounds: This study aimed to evaluate the relationship between neck circumference (NC) and gestational diabetes mellitus (GDM), and the efficacy of NC in predicting GDM by comparing with pregestational body mass index (preBMI) in southern Chinese woman.

Marerials and methods: A total of 371 pregnant women (97 GDM and 274 normal pregnant women) were recruited from the third affiliated hospital of Sun Yat-Sen University, Guangzhou, China. NC was measured at $11\text{-}13^{+6}$ gestational weeks. Gestational diabetes mellitus was diagnosed through a 75-g oral glucose tolerance test at 24–28 gestational weeks. Using the receiver-operator characteristic (ROC) curve analysis, we evaluated the association between NC and GDM.

Results: The area under ROC curves (AUC) were 0.65 (95% confidence interval (CI) 0.60-0.70) for NC and 0.64 (95% CI 0.59-0.69) for preBMI in diagnosing GDM and no difference was found between them ($P = 0.66$). NC ≥ 33.8 cm was determined to be the best cutoff level for identifying subjects with GDM (sensitivity 68.04%, specificity 59.12%). Multivariate logistic regression analysis showed that a large NC in the first trimester was an independent risk factor for the development of GDM (odds ratio (OR) 1.29, 95% CI 1.72-7.45).

Conclusions: NC, as well as preBMI, might be a novel anthropometric index for GDM screening. The increase of NC could be an independent risk factor for GDM in first trimester pregnancy.

Keywords: gestational diabetes mellitus, neck circumference, predicting, receiver-operator characteristic, first trimester pregnancy

Introduction

Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance with onset or first recognition during pregnancy, and it affects approximately 14% of all pregnant women [1, 2]. Many anthropometric indexes have been used for predicting GDM, such as body mass index (BMI), waist circumference (WC) and waist/hip ratio (WHR) [3, 4]. Pre-gestational body mass index (preBMI) is a traditional predictor for GDM [5, 6]. WC is the most commonly used anthropometric indicator for evaluating abdominal adiposity. However, WC has some disadvantages as it varies greatly during pregnancy and it is easily affected by diet, respiratory or health conditions [7].

Neck circumference (NC) is an index for upper-body fat distribution. Upper-body obesity has been proved to be more strongly associated with glucose intolerance, hyperinsulinemia, diabetes and hypertriglyceridemia rather than lower-body obesity [8, 9] . As a new screening measurement, NC is simple, invariable, repeatable and inexpensive, and sometimes it might be a better index for adverse risk profile than WC [10, 11]. Therefore, NC has been evaluated in relation to cardiovascular disease, insulin resistance (IR), and metabolic syndrome (MetS) [12-14]. Women diagnosed with GDM also have hyperglycemia, hyperlipidemia and IR [15]. Whether NC is correlated to GDM still requires exploration, as there is a lack of current studies.

In this study, we aim to evaluate the association between NC and GDM and to compare NC at 11-13^{+6} gestational weeks with preBMI in predicting GDM.

Materials and methods

Subjects

The Human Research Ethics Committee of the third affiliated hospital of Sun Yat-Sen University approved this retrospective study. The data were collected from the third affiliated hospital of Sun Yat-Sen University, Guangzhou, China, from April 2016 to April 2017. A total of 371 singleton pregnant women with complete prenatal care services and delivery in this hospital were available for analysis. Patients with thyroid disease or operations were excluded.

Clinical characteristics

Clinical characteristics (including age, gravidity, parity and family history) were registered by self-report at the first prenatal visit at $11\text{-}13^{+6}$ gestational weeks. Delivery data (including gestational age at delivery, neonatal birth weight and postpartum hemorrhage) were registered in the hospital after delivery.

Anthropometric measurements

All participants underwent a physical examination at $11\text{-}13^{+6}$ gestational weeks. Bodyweight and height were registered by self-report and BMI was calculated by weight (kg) divided by height (m^2). NC was measured according to the standard protocols of the China Chronic Disease and Risk Factor Surveillance 2010. After providing informed consent, subjects stood with the head in the horizontal plane position. Plastic tape was applied below the thyroid cartilage in the front and at the level of the mid cervical spine at the back. The minimum circumference was recorded to the nearest 0.1 cm. Two trained physicians completed a training program and obtained anthropometric measurements.

Laboratory parameters

After an 8 hours overnight fasting, fasting plasma glucose (FPG) and lipid profile including serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were performed at $11\text{-}13^{+6}$ gestational weeks and determined by enzymatic colorimetric tests.

GDM diagnosis

All subjects were asked to return between 24-28 gestational weeks. A 75-g oral glucose tolerance test (75-g OGTT) is defined as the gold standard of GDM diagnosis and the diagnosis criteria was based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [16] that any 1 or more of the following values are met or exceeded the levels: 0 hour (fasting) ≥ 5.10 mmol/L, 1 hour ≥ 10.00 mmol/L and 2 hours ≥ 8.50 mmol/L. After the 75-g OGTT, subjects were divided into GDM group (n=97) or normal control group (n=274).

Statistical analysis

Statistical analysis was performed using the SPSS 19.0 software and $p< 0.05$ was considered statistically significant. Continuous variables were presented as mean (SD) and skewed variables were presented as median (interquartile range). Student's t test for independent samples was used for normally distributed continuous variables. The Mann-Whitney U test was performed for non-normally distributed continuous variables. Receiver operator characteristic (ROC) curve analysis was performed to determine the accuracies of NC and preBMI in predicting GDM. The optimal cut-off point was the point on the ROC curve closest to the (0, 1) point. The areas under the ROC curves (AUC) were calculated and DeLong test [17] was used to compare areas under ROC curves. Multivariate logistic regression analysis was carried out to explore the independent associated factors of GDM (backward method was used).

Results

In total, 371 women completed the study, including 97 GDM women and 274 normal women. The clinical characteristics of the participants are shown in Table 1. GDM group were older, presented greater gravidity and parity, delivered earlier and had more postpartum hemorrhage (P < 0.05). The mean NC (34.3 vs 33.5 cm) and preBMI (21.7 vs 20.6 kg/m^2) were higher in the GDM group than in the normal group (P < 0.05). The GDM group also demonstrated higher plasma glucose levels, including initial FPG, 0 hour, 1 hour and 2 hours plasma glucose on OGTT. However, the initial lipid profile and neonatal birth weight were similar in the 2 groups (P > 0.05).

The ROC curve determines the ability for NC and preBMI to identify GDM. The AUCs were 0.65 (95% CI 0.60-0.70) for NC and 0.64 (95% CI 0.59-0.69) for preBMI (Fig. 1). No significant difference was detected in these 2 AUCs (P = 0.66). The results showed that NC similar to preBMI had the value to predict GDM.

The optimal cut-off point was the point on the ROC curve closest to the (0, 1) point. An NC of 33.8cm yielded the highest combination of sensitivity (68.04%) and specificity (59.12%) (Table 2).

Multivariate logistic regression analysis showed that, considering the confounders in early gestation (including NC, preBMI, maternal age, gravidity and parity), NC and age were independent risk factors for GDM development. The OR value of NC were 1.29(95% CI 1.11-1.50) which meant, with each 1 cm increase in NC, the risk of developing GDM increased a 1.3-fold (Table 3).

Discussion

In the present study, we demonstrated that NC could be used as a novel indicator to predict GDM. The diagnostic accuracy of NC for predicting GDM was similar to that of preBMI. An NC of 33.8 cm might be the optimal cut-point for predicting GDM.

NC is a marker of upper-body subcutaneous fat and has been reported to be correlated well with glycemic status, elevated free fatty acid (FFA), WC, WHR and BMI in nonpregnant populations [14, 18, 19]. Therefore, it has be used as a straightforward and reliable index and sometimes surpass other anthropometric measurements as a powerful marker of visceral adipose tissue (VAT), MetS and IR [14] [20-22]. GDM women also have greater IR and higher BMI and FFA [15]. Whether NC is correlated to GDM remains unclear and the studies are lacking.

In this study, the AUC was 0.65 (95% CI 0.60-0.70) for NC in predicting GDM and this was similar to the traditional predictor preBMI (0.64 (95% CI 0.59-0.69)) in predicting GDM (P = 0.66). To our knowledge, this is the first study to evaluate NC in the first trimester for predicting GDM and compare it with preBMI.

The optimal cut-off point of 33.8 cm yielded the highest combination of sensitivity (68.04%) and specificity (59.12%). He Fang et al [23] reported the AUC of NC (at 16 gestational week) for identifying GDM was 0.65 (95% CI 0.55-0.76), and a NC ≥ 35.15 cm yielded an optimal combination sensitivity of 48.8% and specificity of 77.9%. The AUCs for NC in predicting GDM were very close in these 2 studies, indicated NC might be a good anthropometric index to screen for GDM. In contrast to He Fang et al, the optimal cut-point of NC in our study was lower, and showed a higher sensitivity and lower specificity. However, different studies reporting different sensitivities and specificities at different NC cut points possibly could be due to different study populations, gestational weeks and ethnicity. Larger sample studies and multi-center studies are needed to determine the optimal cut-off value for NC to predict GDM.

There were also some limitations in our study. First, this study is a single-center and small sample study in southern China which may restricted the application of study conclusion. Further study needs to be conducted to confirm our findings. Second, all subjects were asked to report retrospectively on weight and height prior to pregnancy, which were used to calculate preBMI. As the study began after the subjects conception, accurate measurement of pre-gestational weight was hard to obtain. The same problem also exist in other studies too [24-26].

In conclusion, NC, as well as preBMI, might be a new anthropometric index for predicting GDM. The increase of NC may be an independent risk factor for GDM in the first trimester pregnancy.

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Fig.1 ROC curves for determining Neck circumference and pregestational BMI cutoff values for identifying GDM

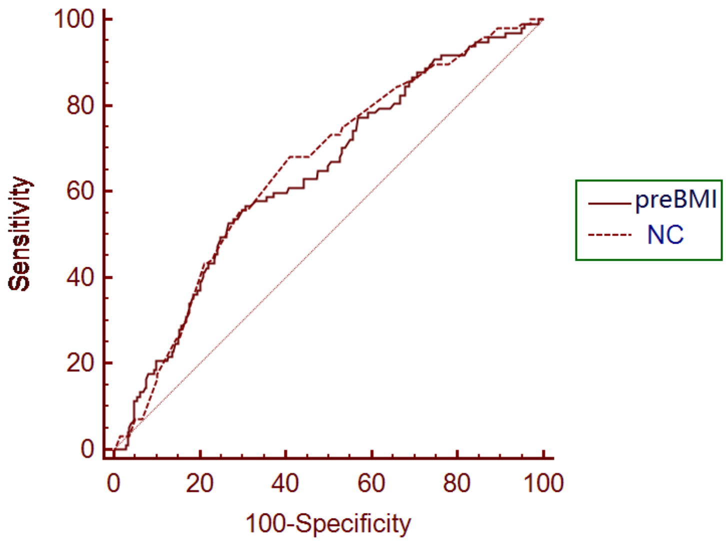

Table 1. Characteristics of the study participants divided by 75-g oral glucose tolerance test*

Characteristics	Total (*n*=371)	Normal (*n*=274)†	GDM (*n*=97)	*P*
Age (years)	30(27-32)	29(26-31)	32(29-35)	0.000
Gravidity	2(1-2)	2(1-2)	2(1-3)	0.000
Parity	1(1-2)	1(1-2)	1.5(1-2)	0.000
Pregestational BMI (kg/m^2)	20.9(2.5)	20.6(2.5)	21.7(2.3)	0.012
Neck circumference (cm)	33.7(1.7)	33.5(1.7)	34.3(1.5)	0.000
FPG(mmol/L)	4.52(0.42)	4.45（4.22-4.72）	4.61（4.33-4.93）	0.003
TG(mmol/L)	1.65(0.63)	1.59(0.60)	2.03(0.77)	0.074
TC (mmol/L)	5.29(0.91)	5.32(0.88)	5.10(1.13)	0.953
HDL(mmol/L)	1.82(0.34)	1.85(0.33)	1.60(0.37)	0.056
LDL(mmol/L)	2.80(0.76)	2.81(0.77)	2.73(0.74)	0.737
OGTT 0 hour(mmol/L)	4.39(4.13-4.58)	4.28(4.11-4.50)	4.42(4.22-4.84)	0.000
OGTT 1 hour (mmol/L)	7.79(1.91)	6.99(6.03-8.20)	10.03(9.28-10.59)	0.000
OGTT 2 hour(mmol/L)	7.04(1.62)	6.37(5.64-7.17)	8.90(8.34-9.66)	0.000
Gestational age at delivery (weeks)	39.19（1.27）	39.29（38.59-40.14）	38.85（38.14-40.00）	0.025
Postpartum hemorrhage(ml)	319（254-350）	285（245-335）	320（275-420）	0.000

Neonatal birth weight (kg)	3.22（1.18）	3.20（2.90-3.45）	3.25（3.00-3.60）	0.156

*Values are mean (SD) or medians (interquartile ranges).

†compared with GDM group

FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol and LDL-C, low-density lipoprotein cholesterol

Table 2. Neck circumference performance as a predictor for gestational diabetes mellitus

Cut point (cm)	Sensitivity (%)(95% CI)	Specificity (%)(95% CI)	+LR	-LR	PPV (%)(95% CI)	NPV (%)(95%CI)
30	100.00（96.3 - 100.0）	2.92（1.3 - 5.7）	1.03	0.00	26.7（22.2 - 31.6）	100.0（59.0 - 100.0）
31	97.94（92.7 - 99.7）	9.49（6.3 - 13.6）	1.08	0.22	27.7（23.0 - 32.8）	92.9（76.5 - 99.1）
32	89.69（81.9 - 94.9）	22.26（17.5 - 27.7）	1.15	0.46	29.0（23.9 - 34.5）	85.9（75.5 - 93.1）
33	75.26（65.5 - 83.5）	46.35（40.3 - 52.4）	1.40	0.53	33.2（27.0 - 39.8）	84.1（77.3 - 89.6）
33.8*	68.04（57.8 - 77.1）	59.12（53.0 - 65.0）	1.66	0.54	37.1（30.0 - 44.6）	83.9（78.0 - 88.8）
34	55.67（45.2 - 65.8）	68.98（63.1 - 74.4）	1.79	0.64	38.8（30.7 - 47.5）	81.5（75.9 - 86.2）
35	27.84（19.2 - 37.9）	83.94（79.0 - 88.1）	1.73	0.86	38.0（26.8 - 50.3）	76.7（71.5 - 81.3）

36	7.22 （3.0 - 14.3）	93.43 （89.8 - 96.1 ）	1.10	0.99	28.0 （12.1 - 49.4 ）	74.0 （69.0 - 78.5）
37	3.09 （0.6 - 8.8）	98.18 （95.8 - 99.4 ）	1.69	0.99	37.5 （8.5 - 75.5）	74.1 （69.3 - 78.5）

* Optimal cut-off point, which showed the highest combination of sensitivity and specificity

+LR, positive likelihood ratio; -LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval

Table 3. Multiple logistic regression analysis NC, preBMI, maternal age, gravidity and parity as confounders of gestational diabetes mellitus*

Items	B	S.E.	Wald	P-value	OR (95% CI)
Age	0.14	0.03	23.83	0.000*	1.15(1.09, 1.22)
Neck circumference	0.26	0.08	10.57	0.001*	1.29(1.11, 1.50)

* Backward method was used, maternal age and preBMI were not in the final model

BMI, body mass index; B, beta coefficient; S.E., Standard Error; CI, confidence interval; OR, odds ratio