

Urinary C-Peptide Secretion(UCPS): Can It be A New Index to Reflect Insulin Sensitivity and A Predictor in Pregnant Women?

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Abstract

Background: In order to assess the correlation between pregnant women's urinary C-peptide secretion(UCPS) and insulin sensitivity, and to examine the predictors of gestational diabetes.

Methods: we recruited 166 women between 20 and 28 weeks of gestation. Their height and weight were measured to calculate the body mass index (BMI). 75g OGTT was carried out, so as to detect the serum glucose, serum insulin and C-peptide levels. Besides, the homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β cell function (HOMA- β), Matsuda index, and area under the serum C-peptide curve (CPauc) were calculated. Additionally, the fasting urine specimen and all urine samples within 2 hours after OGTT were collected to determine the urinary C-peptide and urine volume to calculate UCPS.

Results: We found that Fasting serum insulin (Fins), Fasting serum C-peptide (FCP), BMI, OGTT 2h UCPS(UCPS120), CPauc, Matsuda index and HOMA-IR of GDM group were higher than NGT group. FCP was correlated with UCPS0 ($r=0.234$, $p=0.002$) and HOMA- β ($r=0.251$, $p=0.001$). UCPS120 was correlated with CPauc($r=0.176$ $p<0.001$), Matsuda index($r=-0.362$, $p<0.001$) and HOMA-IR($r=0.336$, $p<0.001$). The combination of BMI and UCPS120 was better than other index in predicting GDM, with a sensitivity of 72.0% and specificity of 70.7%.

Conclusion: UCPS120 had the potential to be a new index to reflect insulin sensitivity in pregnant women. To screening the GDM, the combination of BMI and UCPS120 was better than other index.

1. Background

Gestational diabetes mellitus (GDM) is a global health problem, which is mainly caused by impaired insulin action and β -cell dysfunction [1]. With the progress of pregnancy, maternal insulin sensitivity decreases by about 60 percent [2], and the increasing insulin antagonistic hormone will lead to maternal hyperinsulinemia [3]. In clinical practice, measuring insulin secretion is relatively straightforward using HOMA- β and CPauc. Matsuda index and HOMA-IR are commonly used to evaluate the insulin sensitivity [4, 5].

To diagnose GDM and evaluate the islet function of pregnant women, we usually use the serum glucose, insulin and C-peptide detected in three or more points during OGTT. There are a number of clinical studies to explore relatively simplified indicators. Urinary C peptide is a non-invasive, easily operative, and highly acceptable index [6]. Studies have shown that Urinary C peptide creatinine ratio (UCPCR) is a practical and non-invasive method to assess insulin secretion[7, 8]. But urine creatinine is easily affected by muscle content, which may lead to a higher UCPCR in women[9]. So our study first attempted to use postprandial urinary C-peptide secretion(UCPS) to assess islet function in pregnant women between 20 and 28 weeks of gestation, and to investigate whether it can be used as an indicator for GDM screening.

2. Methods

2.1 Objects

Pregnant Han nationality women at 20-28 gestational weeks (according to Chinese Diabetes Society 2017 guidelines) undergoing routine checks in the outpatient department of our hospital from January 2017 to December 2017 were selected. All of them were preliminarily screened for the 75g OGTT to collect the fasting, 1 h and 2h plasma as well as urine specimens. All participants were then divided into GDM group and NGT group according to the serum glucose level. Those previously diagnosed with diabetes, combined with acute infection, taking glucocorticoids within the past 2 weeks, and combined with other chronic disease were excluded. This study was approved by Ethics Committee, and all enrolled participants had signed the informed consent.

Diagnostic criteria of GDM: according to the recommendations of the guidelines from (2017): pregnant women conforming to any one of the following criteria could be diagnosed: FBG ≥ 5.1 mmol/L (92mg/dL), 75g OGTT 1h serum glucose ≥ 10.0 mmol/L (180mg/dL) or 75g OGTT 2h serum glucose ≥ 8.5 mmol/L (153 mg/dL).

2.2. Methods

1 General clinical data collection: the age, family history of diabetes, history of GDM, previous medical history, gestational week (w), height (m), and current weight (kg) of all enrolled pregnant women were recorded. Meanwhile, the current body mass index (BMI kg/m²) was calculated.

2 Blood specimen collection and determination: for all enrolled pregnant women, 5ml fasting blood was collected at 8:00 in the morning after an 8h overnight fast, so as to determine the FBG, blood lipid, liver and kidney function, glycated hemoglobin (HbA1c), fasting insulin (FIns), and fasting C-peptide (FCP). After fasting blood collection, 75g oral glucose tolerance test (OGTT) was taken, the venous blood was collected at 1h and 2h respectively, so as to determine the serum glucose, serum insulin and serum C-peptide at corresponding time points.

3 Urine specimen collection and determination: the fasting urine (the participants should passed their overnight first void urine before OGTT), as well as urine at OGTT 2h (all urine should be collected until 2h after taking the glucose) were collected. No food was allowed during the OGTT, while water was allowed. The urine volume should be recorded each time, and 10 ml urine should be retained, which was transferred to the 5 ml frozen tubes and preserved in the refrigerator at -80°C until detection.

4 Determination of related indexes: Determination of serum insulin, serum C-peptide and urine C-peptide: chemiluminescent immunoassay (IMMULITE 2000 analyzer, Siemens); serum glucose determination: glucose oxidase method (AU5800 biochemical analyzer, Beckmann); HbA1c determination: high pressure liquid chromatography (HPLC) (Arkray HA-8180 full- automatic glycated hemoglobin analyzer, Arkray Kabushiki gaisha); and urine creatinine determination: picric acid method (AU5800 biochemical analyzer, Beckmann).

5 computational formula: Matsuda index = $10000 / \sqrt{[(18 \times \text{FBG (mmol/L)} \times \text{Fins (mU/L)} \times \text{OGTT the average serum glucose (mmol/L)} \times \text{OGTT the average insulin (mU/L)})]}$ HOMA-IR (homeostasis model of insulin resistance index) = $\text{Fins (mU/L)} \times \text{FBG (mmol/L)} / 22.5$; HOMA- β (homeostasis model of insulin secretion index) = $[20 \times \text{Fins (mU/L)}] / [\text{FBG (mmol/L)} - 3.5]$; UCPS (product of urine volume and urinary C peptide) (ug) = $\text{UCP (ng/mL)} \times \text{urine volume (mL)} / 1000$.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 13.0. A p value of ≤ 0.05 was considered statistically significant. Measurement data were expressed as mean \pm standard deviation, and inter-group comparison was carried out using t test. For non-normal distribution data, Mann-Whitney U test was employed for comparison. The Pearson correlation coefficient and linear regression models were adopted for correlation analysis. Receiver operator characteristic curve (ROC) was used to assess the predictive ability for GDM of each index.

3. Results

3.1. General information of participants (Table 1): 166 pregnant women were enrolled into this study, which were all Han nationality. 41 were diagnosed with GDM, 21 with family history of diabetes, accounting for 24.7% and 12.7% of all participants, respectively. There were no significant differences in age, gestational age and family history of diabetes between the two groups.

Table 1
Participants Characteristics and comparisons between two groups

	Min	Max	NGT (N = 125)	GDM (N = 41)	<i>p</i>
Age(years)	21	40	27.70 ± 3.66	28.20 ± 3.84	0.462
Gestational age(weeks)	20	28	25.51 ± 1.42	25.85 ± 1.68	0.475
Family history of diabetes(%)	/	/	15(12.0%)	6(14.6%)	1.000
BMI(kg/m ²)	16.02	34.38	20.31 ± 2.71	22.13 ± 2.63	< 0.001**
Fins(uU/mL)	2.04	46.04	7.42 ± 3.22	10.40 ± 6.84	0.014*
FCP(ng/mL)	0.72	6.14	1.87 ± 0.67	2.51 ± 0.84	0.001**
FBG(mmoL/L)	4.09	6.01	4.62 ± 0.25	5.23 ± 0.31	< 0.001**
Ins60(uU/mL)	12.67	352.66	52.90 ± 36.97	71.42 ± 56.92	0.076
CP60(ng/mL)	3.59	35.62	9.94 ± 3.73	12.20 ± 5.02	0.016*
BG60(mmoL/L)	4.05	11.90	7.31 ± 1.43	9.09 ± 1.62	< 0.001**
Ins120(uU/mL)	10.37	315.45	51.27 ± 36.28	73.27 ± 56.22	0.114
CP120(ng/mL)	4.61	22.97	10.95 ± 4.00	12.70 ± 4.60	0.135
BG120(mmoL/L)	3.95	9.32	6.55 ± 0.94	7.68 ± 1.26	< 0.001**

p* < 0.05; *p* < 0.01

BMI: body mass index;GDM: Gestational Diabetes Mellitus;HbA1c: Glycosylated hemoglobin;

Fins: Fasting Insulin; Ins60: OGTT 1-Hour Insulin; Ins120: OGTT 2-Hour Insulin;

FCP: Fasting C peptide; CP60: OGTT 1-Hour C peptide; CP120: OGTT 2-Hour C peptide;

FBG: Fasting Glucose; BG60: OGTT 1-Hour Glucose; BG120: OGTT 2-Hour Glucose;

UCPS0: Fasting UCPS; UCPS120: OGTT 2Hour UCPS;

HOMA-β: Homeostasis model assessment of beta cell function;

HOMA-IR: Homeostasis model assessment for insulin resistance;

CPauc: C peptide area under the curve; INSauc: Insulin area under the curve.

	Min	Max	NGT (N = 125)	GDM (N = 41)	<i>p</i>
UCPS0(ug)	0.36	27.86	4.76 ± 4.57	5.74 ± 4.19	0.510
UCPS120(ug)	1.19	51.37	11.34 ± 65.06	17.36 ± 10.78	0.033*
HbA1C(%)	3.90	5.60	4.82 ± 0.25	5.09 ± 0.22	< 0.001**
HOMA-β	54.60	601.83	133.53 ± 51.56	122.76 ± 87.97	0.106
HOMA-IR	0.38	10.29	1.54 ± 0.71	2.43 ± 1.58	< 0.001**
Matsuda	0.86	18.01	32.37 ± 13.56	21.33 ± 9.20	< 0.001**
CPauc	446.40	2907.90	981.15 ± 322.46	1187.69 ± 400.53	0.014*
INSauc	1353.60	32004.30	4934.84 ± 3125.91	6795.46 ± 5057.21	0.058
<i>*p</i> < 0.05; <i>**p</i> < 0.01					
BMI: body mass index;GDM: Gestational Diabetes Mellitus;HbA1c: Glycosylated hemoglobin;					
Fins: Fasting Insulin; Ins60: OGTT 1-Hour Insulin; Ins120: OGTT 2-Hour Insulin;					
FCP: Fasting C peptide; CP60: OGTT 1-Hour C peptide; CP120: OGTT 2-Hour C peptide;					
FBG: Fasting Glucose; BG60: OGTT 1-Hour Glucose; BG120: OGTT 2-Hour Glucose;					
UCPS0: Fasting UCPS; UCPS120: OGTT 2Hour UCPS;					
HOMA-β: Homeostasis model assessment of beta cell function;					
HOMA-IR: Homeostasis model assessment for insulin resistance;					
CPauc: C peptide area under the curve; INSauc: Insulin area under the curve.					

3.2. Fins, FCP, BMI (before pregnant), UCPS120, CPauc, Matsuda index and HOMA-IR of GDM group were higher than NGT group (Table 1).

3.3. FCP was correlated with UCPS0 ($r=0.243$, $p=0.002$) and HOMA-β($r=0.251$, $p=0.001$)(Figure 1A, 1B).

3.4. UCPS120 was correlated with Matsuda index ($r=-0.362$, $p<0.001$) and HOMA-IR ($r=0.336$, $p<0.001$) (Figure 2A, 2B).

3.5. UCPS120 was correlated with CPauc ($r=0.176$, $p<0.001$) (Figure3).

3.6. To predict the GDM, we try to use the simple and non-invasive index, so BMI, UCPS120, HOMA-IR and Matsuda index are put into the model. The combination of BMI and UCPS120 was better than other index, with a sensitivity of 72.0% and specificity of 70.7% (Table 2, Figure 4).

Table 2
ROC analysis to assess the predictive ability for GDM of each index

variable	AUC	Standard error	P	95% credibility interval	
				lower	upper
BMI	0.713	0.043	< 0.001	0.628	0.799
UCPS120	0.670	0.053	0.001	0.567	0.774
HOMA-IR	0.735	0.043	< 0.001	0.651	0.819
Matsuda	0.752	0.042	< 0.001	0.669	0.834
BMI + UCPS120	0.762	0.042	< 0.001	0.679	0.846
BMI + HOMA-IR	0.763	0.039	< 0.001	0.687	0.839
BMI + Matsuda	0.757	0.042	< 0.001	0.676	0.839
BMI: body mass index;GDM: Gestational Diabetes Mellitus;UCPS120: OGTT 2Hour UCPS;					
HOMA-β: Homeostasis model assessment of beta cell function;					
HOMA-IR: Homeostasis model assessment for insulin resistance;					

4. Discussion

UCPS is a new index adopted in this study, which reflects the total secretion of C-peptide in urine within a certain period of time, while different from UCPCR. In our study, UCPS0 was associated with FCP and HOMA-β, but the r value was low. In other study, they asked all the women to pass their overnight first void urine and collect the second void urine. We didn't emphasize to collect the second void urine, it may resulted in some discrepancy. UCPS120 of OGTT was correlated with CPauc, Matsuda index and HOMA-IR, and the Matsuda index had the strongest correlation. Previous study showed that Matsuda index had stronger correlation with hyperinsulinaemic-euglycaemic clamp in pregnant women [10]. Although UCPCR120 only had weak correlation with Matsuda index, due to the small sample size, it still had the potential to be a new index to reflect insulin sensitivity in pregnant women.

Comparing the indexes of the two groups, it was found that the BMI, UCPS120, Fins, FCP, CPauc, Matsuda index and HOMA-IR of the GDM group were significantly higher than the NGT group. In all of these indexes, the calculation of CPauc, Matsuda index and HOMA-IR requires more parameters. The determination of these parameters requires multiple blood tests. while BMI and UCPS120 are non-invasive ones. HOMA-IR and Matsuda index had better predictions for GDM in previous studies [11, 12].

Recently researches showed that the pregnant women with high BMI before pregnancy had significantly high risk in GDM [13]. And pregnancy high BMI may be the independent risk factor for GDM [14]. We hope to use effective, simple and best non-invasive index to predict the GDM. So we choose BMI, UCPS120, HOMA-IR and Matsuda index. ROC curve analysis showed that to predict the GDM, the combination of BMI and UCPS120 was better than other index, with a sensitivity of 72.0% and specificity of 70.7%. Many hospitals in china now advocate 75 g OGTT for all pregnant women, but multiple blood collection during pregnancy may cause problems for some women. If non-invasive tests can be used to screen out high-risk groups, and then OGTT tests for high-risk groups, it may help to reduce the psychological pressure of pregnant women, but also to save medical resources.

There are still some limitations in this study, all women included were in the second trimester of pregnancy (20–28 weeks), and the sample size was small. The conclusion needs to be expanded to verify the sample size. Secondly, the women included in this study were all with normal renal function, and the effect of different renal function status on this index could not be determined. There is increasing evidence that lifestyle and therapeutic intervention after 18 weeks of pregnancy in at-risk women has little effect on preventing both GDM and fetal macrosomia [15–18]. Further studies on a larger scale are needed, such as women with different renal function states in the early stage of pregnancy, to evaluate whether UCPS can be applied to women in early pregnancy to facilitate early screening of high-risk populations and early intervention.

5. Conclusion

UCPS120 had the potential to be a new index to reflect insulin sensitivity in pregnant women. To screening the GDM, the combination of BMI and UCPS120 was better than other index.

Abbreviations

GDM	gestational diabetes mellitus
UCPs	Urinary C-peptide secretion
OGTT	Oral glucose tolerance test
HOMA-IR	Homeostasis model assessment for insulin resistance
HOMA- β	Homeostatic model assessment of beta cell function
UCPCR	urinary C peptide/creatinine ratio
AUC	Area under the curve
SPSS	Statistical package for the social sciences
BMI	Body mass index
Fins	Fast insulin
FCP	Fast C-peptide
FBG	Fast blood glucose
Ins	Insulin
CP	C peptide
BG	Blood glucose
HbA1C	Glycosylated hemoglobin
WHO	Worlds health organization
ADA	American diabetes association
CDS	Chianese diabetes society
UCR	Urinary creatinine
ROC	Receiver operator characteristic curve
HPLC	High pressure liquid chromatography

Declarations

Ethics approval and consent to participate

This study was approved by Wuhu Second People's Hospital Ethics Committee, and all enrolled participants had signed the informed consent.

Consent for publication

Not applicable

Competing interests

There is no conflict of interest to disclose.

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Authors' contributions

WZ and XHM performed the collection of clinical specimens. All authors contributed to the concept and writing of the article. All authors read and approved the final manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated for the current study.

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Figures

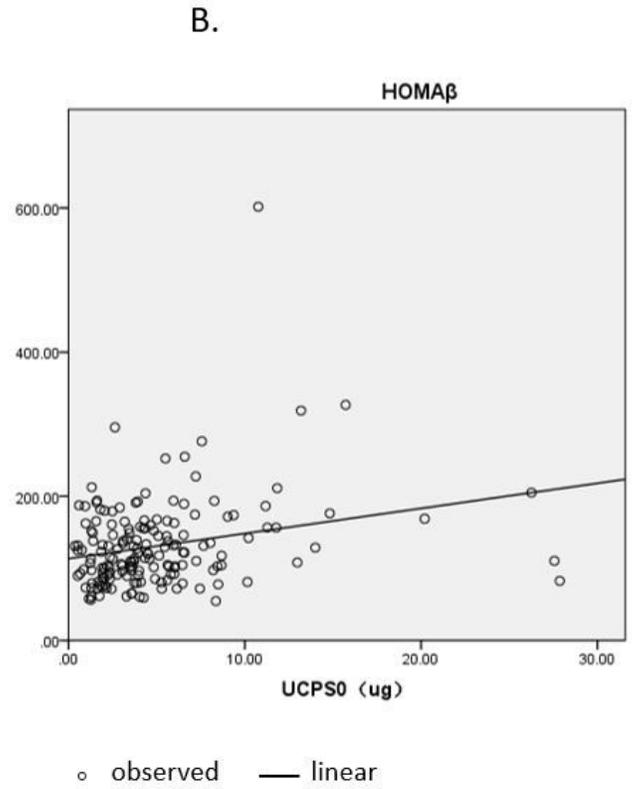
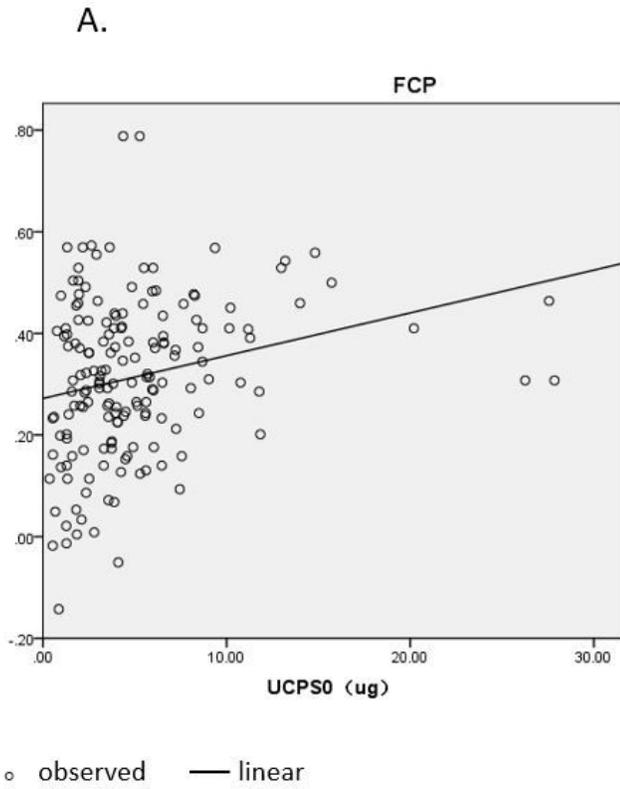


Figure 1

A. Linear regression model for UCPS0 and FCP, $Y=0.272+0.08X$, $r=0.243$, $p=0.002$. B. Linear regression model for UCPS0 and HOMAβ, $Y=113.434+3.487X$, $r=0.251$, $p=0.001$, FCP: fasting C peptide, UCPS0: fasting urinary C peptide secretion.

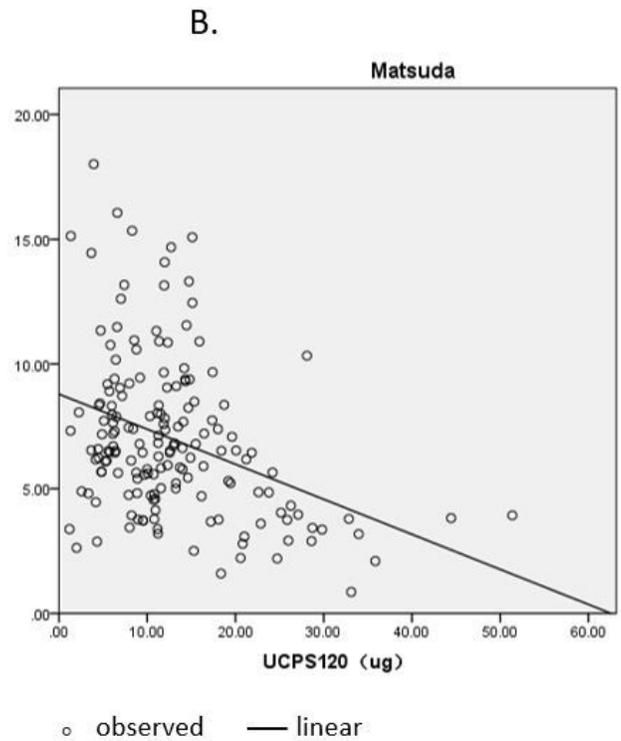
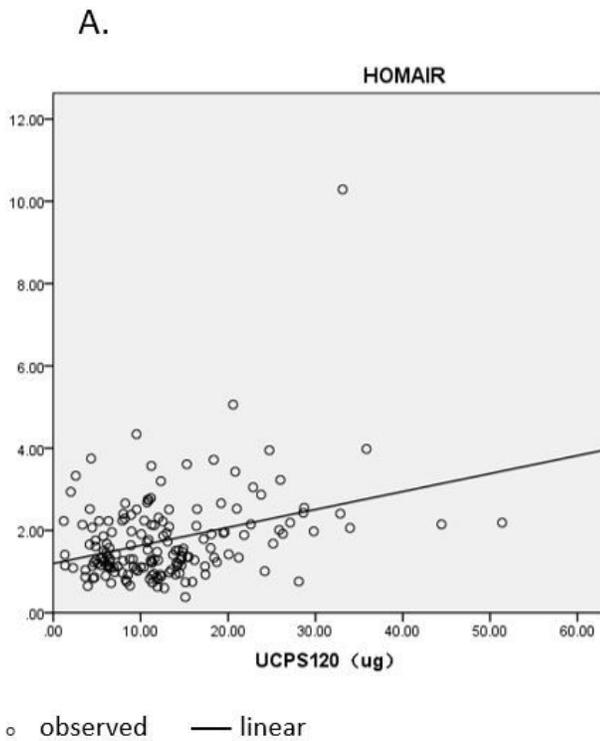


Figure 2

A. Linear regression model for UCPS120 and HOMA IR, $Y=1.199+0.44X$, $r=0.336$, $p<0.001$. B. Linear regression model for UCPS120 and Matsuda, $Y=8.790-0.141X$, $r=-0.362$, $p<0.001$. UCPS120: OGTT 2h urinary C peptide secretion.

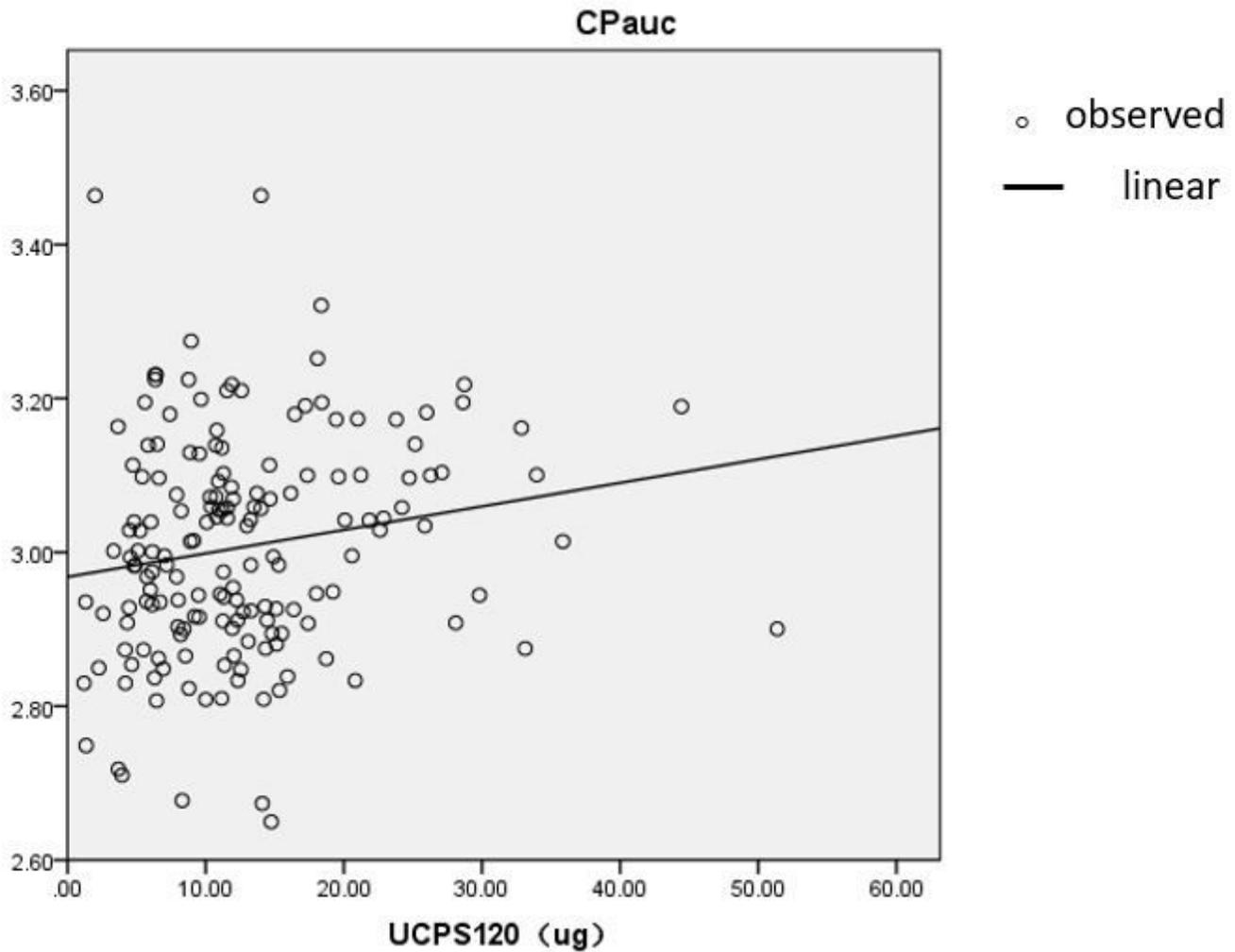


Figure 3

Linear regression model for UCPS120 and CPauc, $Y=2.968+0.003X$, $r=0.176$, $p=0.012$. CPauc: area under the serum C-peptide curve C peptide, UCPS120: OGTT 2h urinary C peptide secretion.

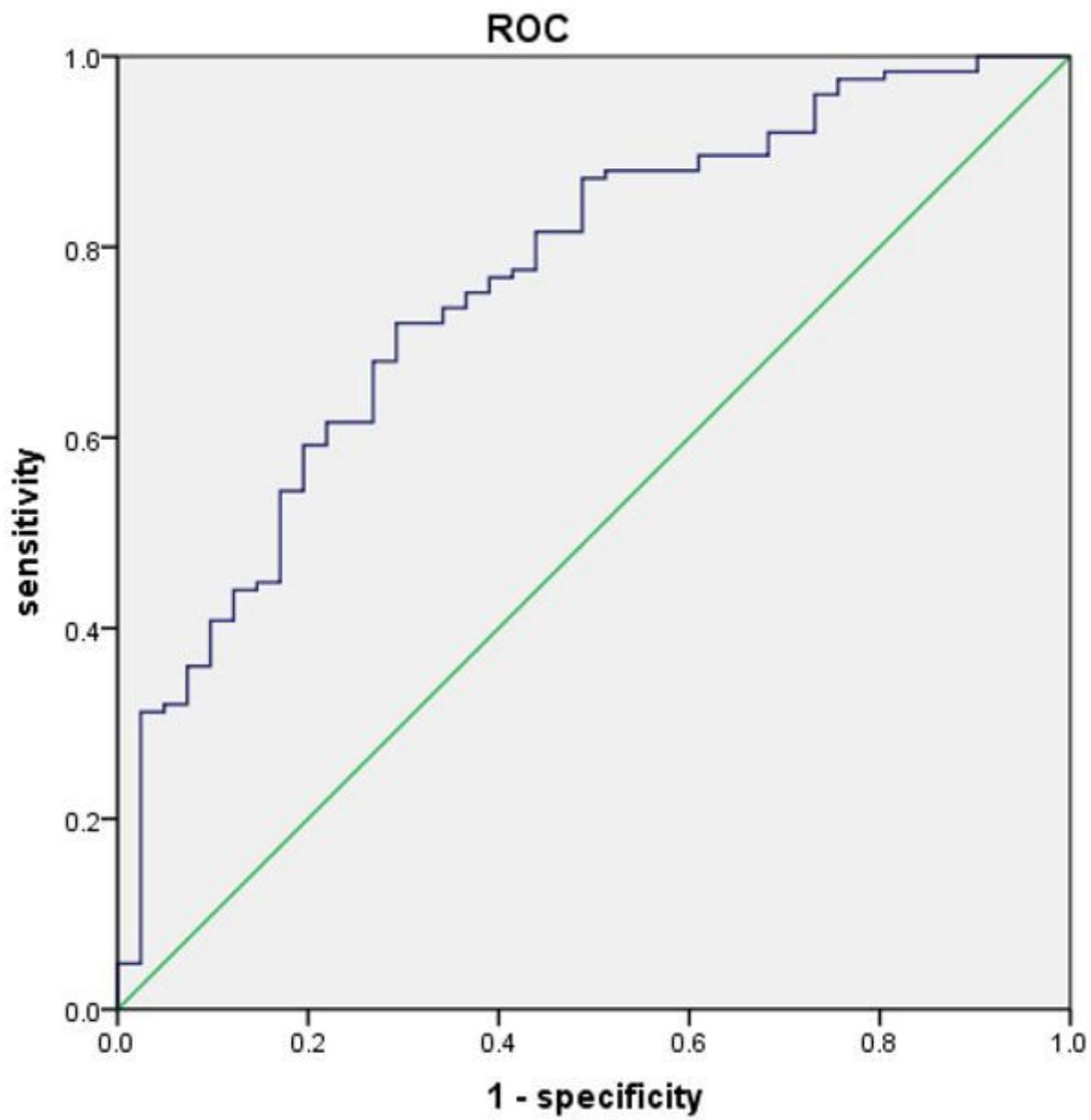


Figure 4

ROC of BMI combined with UCPS120 to predict the GDM