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ORIGINAL RESEARCH

Study on the Relationship and Predictive Value of First-Trimester Pregnancy-Associated Plasma Protein-A, Maternal Factors, and Biochemical Parameters in Gestational Diabetes Mellitus: A Large Case-Control Study in Southern China Mothers

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Objective: To investigate the relationship and predictive value of first-trimester pregnancy-associated plasma protein A (PAPP-A), maternal factors, and biochemical parameters with gestational diabetes mellitus (GDM) in southern China mothers.

Methods: This study recruited 4872 pregnant women. PAPP-A, the free beta subunit of human chorionic gonadotropin (free β-HCG), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), and high- and low-density lipoproteins (HDL, LDL) were measured at 11–13^{+} weeks of gestation. GDM was diagnosed based on a 75 g oral glucose tolerance test at 24–28 weeks of gestation. We performed stepwise logistic regression analysis to determine the odds ratio (OR) and the 95% confidence interval (CI) of GDM. We used Receiver Operating Characteristic (ROC) curves with the area under the curve (AUC) to evaluate the predictive value of PAPP-A, maternal factors, and biochemical markers. The significance of the differences between the AUC values was assessed using the DeLong test.

Results: GDM was diagnosed in 750 (15.39%) women. Independent factors for GDM were age, pre-gestational BMI, GWG before a diagnosis of GDM, previous history of GDM, family history of diabetes, FPG, TG, LDL, PAPP-A, and TC. The AUC of PAPP-A was 0.56 (95% CI 0.53–0.58). The AUC of a model based on combined maternal factors, biochemical markers, and PAPP-A was 0.70 (95% CI 0.68–0.72). Differences in AUC values between PAPP-A alone and the model based on combined maternal factors, biochemical markers, and PAPP-A were statistically significant ($Z= 9.983$, $P<0.001$).

Conclusion: A Low serum PAPP-A level in the first trimester is an independent risk factor for developing GDM later in pregnancy. However, it is not a good independent predictor although the predictive value of a low serum PAPP-A level increases when combined with maternal factors and biochemical markers.

Keywords: gestational diabetes mellitus, pregnancy-associated plasma protein-A, maternal factors, biochemical markers, predictive value

Introduction

Gestational diabetes mellitus (GDM) is defined as the development of carbohydrate intolerance during pregnancy and is one of the most common medical complications of pregnancy.[1,2] The prevalence of GDM is increasing worldwide as obesity and lifestyles change along with delayed childbearing age.[3–5] The adverse effects of GDM on the mother and fetus include polyhydramnios, infection, postpartum hemorrhage, abortion, preterm birth, macrosomia, fetal distress, stillbirth, cesarean deliveries, and

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hypertensive disorders of pregnancy.[1,2] Neonatal morbidities associated with GDM include birth injury, respiratory distress syndrome, hypoglycemia, polycythemia, or hyperbilirubinemia.[1,2] Women with a history of GDM are at increased risk of future diabetes, predominantly type 2.[2] GDM has been implicated in the increased incidence of diabetes and cardiovascular disease in general[6] and type 2 diabetes in offspring.[7]

Risk factors associated with GDM include advanced maternal age, obesity, multiparity, history of GDM, family history of diabetes, high-risk race or ethnicity, and others.[2,8] Screening in early pregnancy for GDM is suggested in women with high-risk factors.[2] However, the best screening test for early detection of GDM is unclear, and the cut-off point for detection before 24 weeks is also unclear.[8–10]

To date, universal screening and diagnosis of GDM are performed mainly between 24 and 28 weeks of gestation, delaying the diagnosis or often making the diagnosis after complications occur.[8–10]

Even though low- or middle-income countries account for 80% of the global diabetes burden, most pregnant women are not screened for GDM.[1] Although earlier prediction could reduce the incidence of adverse pregnancy outcomes,[8–11] there are no effective and convenient predictors of GDM in the first trimester. Li et al previously reported that the FPG level in the first trimester is related to the development of GDM in the middle of the gestational period.[12] Many studies have shown that maternal dyslipidemia is frequently associated with GDM.[13] However, there is no consensus on the relationship between each parameter and GDM.[14–16] Recent studies[17–20] have shown that a low level of pregnancy-associated plasma protein A (PAPP-A) is associated with adverse perinatal outcomes, including abortion, preeclampsia, intrauterine growth restriction, and small for gestational age (SGA). PAPP-A, produced by the placental syncytiotrophoblast, combined with the free beta subunit of human chorionic gonadotropin (free β-HCG), is a parameter to detect Down syndrome. PAPP-A interacts with insulin-like growth factors and helps moderate invasion by placental trophoblast and fetal growth.[17] However, studies of an association between PAPP-A in the first trimester and GDM have produced mixed results.[21–28]

The present large case-control study aimed to investigate the relationship and predictive value of first-trimester pregnancy-associated plasma protein A (PAPP-A), maternal factors, and biochemical parameters with gestational diabetes mellitus (GDM) diagnosed at 24 to 28 weeks of gestation in southern China mothers, to provide evidence for early intervention in the prevention and treatment of GDM.

Materials and Methods

This was a retrospective, case-control, observational study of 4872 pregnant women in southern China who attended the Third Affiliated Hospital of Sun Yat-Sun University, Guangzhou, between 01 January 2017 and 31 December 2018. Inclusion criteria were: (a) women had a singleton pregnancy, (b) with a first prenatal visit before 13^{+6} weeks of gestation, and (c) received regular prenatal care services at this hospital. Exclusion criteria were: (a) fetal loss (abortion or fetal abnormalities), (b) history of chronic diseases (eg, diabetes mellitus, cardiovascular disease, or systemic lupus erythematosus), (c) use of drugs that could influence blood glucose levels (eg, corticosteroids) (Figure 1).

The following maternal information (maternal factors) was obtained from the medical records of all subjects at the first prenatal visit before 13^{+6} weeks of gestation: age, pre-gestational weight, gravidity, height, parity, medical history, last menstrual period (LMP), ultrasound in the first trimester, and mode of conception. LMP and ultrasound established gestational age in the first trimester. Gestational weight gain (GWG) before a diagnosis of GDM was obtained from the prenatal medical records. The pre-gestational body mass index (pre-gestational BMI) was calculated as weight (kg) divided by height squared (m^2).

Serum samples were obtained at 11 to 13^{+6} weeks of gestation, in the morning after an 8-hour fast. Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), and high and low-density lipoproteins (HDL, LDL) were measured using an automated biochemical analysis instrument (Hitachi 7600). PAPP-A and free β-HCG were examined using a time-resolved fluorescence immunoassay (Guangzhou Fenghua Bioengineering LTD TALENT0-STAR). The concentrations of PAPP-A and free β-HCG are presented as a multiple of the median (MoM). A one-step 75-g oral glucose tolerance test (OGTT) was performed at 24 to 28 weeks of gestation. Diagnostic criteria for GDM were according to the International Association for Diabetes in Pregnancy Society Group (IADPSG). Specifically, GDM was confirmed if the 75 g OGTT results were ≥5.1 mmol / L at baseline, ≥10.00 mmol / L at 1 hour, or ≥8.5 mmol. A total of 750 pregnant women were included in the GDM group and 4122 in the control group.

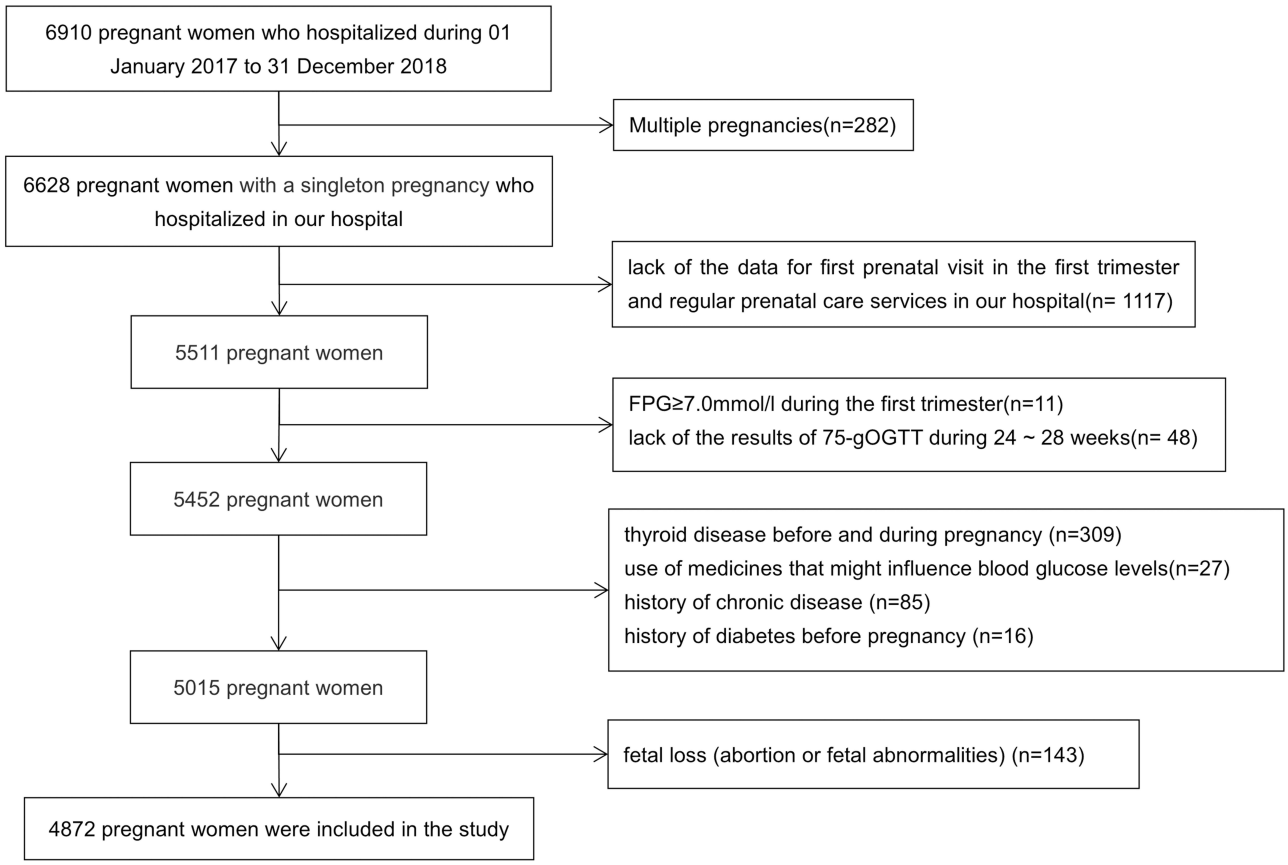

Figure 1 Flow chart showing the subjects selected for the study.
Abbreviations: FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

All statistical analyses were performed with SPSS 22.0 software (IBM SPSS Statistics). All data were analyzed using the Kolmogorov–Smirnov test for normal distribution. All data in this study were non-normally distributed. Continuous data are presented as medians (interquartile range, 25–75%). Categorical data are shown as frequencies and percentages. Data were compared between groups using the Mann–Whitney *U*-tests for continuous data and chi-squared tests for categorical data. Stepwise logistic regression was performed to determine the odds ratio (OR) and the 95% confidence interval (CI) of GDM. Analyses of the receiver operating characteristic (ROC) curves produced the values for predicting GDM. The predictive values for the markers of GDM were compared using the AUCs, and the significance of the differences between them was evaluated using the method described by DeLong.[29,30] Significant variables ($p < 0.05$) were included in the regression model for analysis.

Results

The study population comprised 4872 pregnant women, of whom 750 (15.39%) developed GDM (Table 1). The age and pre-gestational BMI of the women with GDM [31.97 (29.09–35.34) y; 21.04 (19.42–23.11) kg/m^2, respectively] were higher than those of the women without GDM [normoglycemic control;30.28 (28.01–33.11) y; 20.20 (18.75–21.97) kg/m^2; both $p < 0.001$]. The GWG before the diagnosis of women with GDM [7.00 (5.50–9.00) kg)] was higher than that of control women [7.00 (5.40–8.50) kg; $p < 0.05$]. Women with GDM were significantly more likely to be multiparous than the control group (56.40% vs 43.60%; $p< 0.001$). The GDM group was significantly more likely than the control group to have a family history of diabetes (12.40% vs 4.15%) and a previous history of GDM (1.73% vs 0.29%; $p < 0.001$, both). However, the GDM and control groups were comparable in the mode of conception (4.40% vs.3.08%; $p >0.05$).

The following biochemical markers of the two groups were compared (Table 2): FPG, TC, TG, HDL, LDL, PAPP-A, and free β-HCG. Women with GDM had significantly higher levels of FPG, TC, TG, and LDL [4.67 (4.44–4.97) mmol/l, 4.69 (4.11–5.25) mmol/l, 1.23 (0.94–1.64) mmol/l, 2.45 (1.99–2.88) mmol/l] than the control group [4.59 (4.37–4.83) mmol/l, 4.55 (4.05–5.15)

Table 1 Baseline Characteristics of the Subjects

	GDM	Normoglycemic Control	Z/χ^2	*P*
Subjects, n	750	4122		
Age, y†	31.97 (29.09–35.34)	30.28 (28.01–33.11)	9.519	<0.001*
Pre-gestational BMI, kg/m^2†	21.04 (19.42–23.11)	20.20 (18.75–21.97)	7.946	<0.001*
GWG before GDM diagnosis, kg	7.00 (5.50–9.00)	7.00 (5.40–8.50)	3.395	0.001*
Parity, n (%)			40.920	<0.001*
Nullipara	328 (43.73%)	2325 (56.40%)		
Multipara	422 (56.27%)	1797 (43.60%)		
Assisted reproductive technology, n (%)	33 (4.40%)	127 (3.08%)	3.210	0.074
Family history of diabetes, n (%)	93 (12.40%)	171 (4.15%)	67.286	<0.001*
Previous history of GDM, n (%)	13 (1.73%)	12 (0.29%)	18.179	<0.001*

Notes: *$P < 0.05$ compared with normoglycemic control. †Values are expressed as the median (interquartile range).
Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; GWG, gestational weight gain.

Table 2 Biochemical Markers, PAPP-A, and Free β-HCG of the Study Participants in the First Trimester

	GDM	Normoglycemic Control	*Z*	*P*
Subjects, n	750	4122		
FPG, mmol/L	4.67 (4.44–4.97)	4.59 (4.37–4.83)	7.104	<0.001*
TC, mmol/L	4.69 (4.11–5.25)	4.55 (4.05–5.15)	2.860	0.004*
TG, mmol/L	1.23 (0.94–1.64)	1.11 (0.87–1.41)	6.888	<0.001*
HDL, mmol/L	1.62 (1.40–1.84)	1.66 (1.46–1.89)	−3.430	0.001*
LDL, mmol/L	2.45 (1.99–2.88)	2.30 (1.94–2.71)	4.283	<0.001*
PAPP-A, MoM	0.86 (0.59–1.20)	0.97 (0.68–1.27)	−4.947	<0.001*
Free β-HCG, MoM	1.11 (0.76–1.67)	1.17 (0.81–1.73)	−2.944	0.019*

Note: *$P < 0.05$ compared with normoglycemic control.
Abbreviations: GDM, gestational diabetes mellitus; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoproteins; LDL, low-density lipoproteins; PAPP-A, pregnancy-associated plasma protein A; β-HCG, beta-subunit of human chorionic gonadotropin.

mmol/l, 1.11 (0.87–1.41) mmol/l, 2.30 (1.94–2.71) mmol/l, respectively]. Levels of PAPP-A, free β-HCG, and HDL of the GDM group [0.86 (0.59–1.20) MOM, 1.11 (0.76–1.67) MOM, 1.62 (1.40–1.84) mmol/l, respectively] were significantly lower than those of the control [0.97 (0.68–1.27) MOM, 1.17 (0.81–1.73) MOM, 1.66 (1.46–1.89) mmol/].

The maternal factors and biochemical markers were the independent variables with differences between the two groups, and GDM was the dependent variable in the stepwise logistic regression performed to determine the odds ratio (OR) and the 95% confidence interval (CI) of GDM. The results identified maternal age, pre-gestational BMI, GWG before a diagnosis of GDM, family history of diabetes, previous history of GDM, FPG, TG, TC, LDL, and PAPP-A (P<0.05) as significant independent factors for the occurrence of GDM (Table 3).

The ROC curves and AUCs determined the ability of the markers to predict GDM. The AUC was 0.56 (95% CI 0.53–0.58) for PAPP-A, 0.58 (95% CI 0.56 - (95% CI 0.56–0.60) for FPG, 0.58 (95% CI 0.56–0.60) for TG, 0.53 (95% CI 0.51–0.56) for TC and 0.55 (95% CI 0.53–0.57) for LDL. The AUCs for a model based on maternal factors (age + pre-gestational BMI + GWG before GDM diagnosis, + family history of diabetes+ previous history of GDM) and biochemical markers (FPG + TG + TC + LDL) were 0.66 (95% CI 0.64–0.68), and 0.62 (95% CI 0.60–0.64) respectively. The AUC of the combined maternal factors, biochemical markers, and PAPP-A was 0.70 (95% CI 0.68–0.72) (Table 4). Similarly, differences in AUC values between PAPP-A and combined maternal factors, biochemical markers, and PAPP-A were also compared. The difference between them was statistically significant (Z= 9.983, P<0.001) (Figure 2).

The optimal cut-off point was the point on the ROC curve closest to the (0, 1) point. The PAPP-A value of 0.83 MOM was the optimal cut-off point with the highest combination of sensitivity (52.7%) and specificity (37.1%). FPG was 5.07 mmol/l with sensitivity (19.9%) and specificity (91.4%), TG was 1.25 mmol/l with sensitivity (49.1%) and specificity

Table 3 Stepwise Logistic Regression Analysis of Risk Factors for GDM

	β	SE	OR (95% CI)	*P*
Age	0.077	0.010	1.08 (1.06–1.10)	<0.001
Pre-gestational BMI	0.083	0.016	1.09 (1.05–1.12)	<0.001
GWG before GDM diagnosis	0.081	0.015	1.08 (1.05–1.12)	<0.001
Family history of diabetes	1.169	0.144	3.22 (2.43–4.27)	<0.001
Previous history of GDM	1.378	0.438	3.97 (1.68–9.37)	0.002
FPG	0.858	0.102	2.36 (1.93–2.88)	<0.001
TG	−0.245	0.093	1.61 (1.39–1.87)	<0.001
TC	0.477	0.076	0.78 (0.65–0.94)	0.008
LDL	0.428	0.115	1.53 (1.22–1.92)	0.001
PAPP-A	−0.311	0.097	0.73 (0.61–0.89)	0.001
Constant	−10.747	0.730	–	–

Abbreviations: OR, odds ratio; GDM, gestational diabetes mellitus; BMI, body mass index; GWG, gestational weight gain; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoproteins; PAPP-A, pregnancy-associated plasma protein A.

Table 4 ROC Curve Analysis of the Efficacies of Parameters in Predicting GDM

	AUC	95% CI	*P*
PAPP-A	0.56	0.53–0.58	<0.001
Maternal factors	0.66	0.64–0.68	<0.001
Biochemical markers	0.62	0.60–0.64	<0.001
FPG	0.58	0.56–0.60	<0.001
TG	0.58	0.56–0.60	<0.001
TC	0.53	0.51–0.56	0.002
LDL	0.55	0.53–0.57	<0.001
PAPP-A +Maternal factors + Biochemical markers	0.70	0.68–0.72	<0.001

Notes: Maternal factors: age, pre-gestational body mass index, gestational weight gain before GDM diagnosis, family history of diabetes, and previous history of GDM. Biochemical markers: fasting plasma glucose, total cholesterol, triglycerides, low-density lipoprotein.

Abbreviations: AUC, areas under the ROC curves; CI, confidence interval; PAPP-A, pregnancy-associated plasma protein A; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoproteins.

(62.7%), TC was 4.71 mmol/l with sensitivity (49.6%) and specificity (58.2%), LDL was 2.45 mmol/l with sensitivity (50.46%) and specificity (59.3%), respectively (Tables 5–9).

Discussion

This large retrospective case-control study investigated potential biomarkers of GDM that could be used in the first trimester to facilitate early diagnosis. The study examined the predictive value of maternal factors, biochemical markers, and PAPP-A. First, the study found that the rate of GDM in pregnant women in southern China was 15.39% [compared to the 14.8% (95% CI 12.8–16.7%)] rate in mainland China.[31] Furthermore, women with GDM had much lower PAPP-A levels in early pregnancy compared to women who did not develop GDM. Stepwise logistic regression analysis showed that a low PAPP-A level in the first trimester was a risk factor for developing GDM later in pregnancy. The AUC of PAPP-A for predicting GDM was 0.56 (95% CI 0.53–0.58). The AUC of combined maternal factors, biochemical markers, and PAPP-A was 0.70 (95% CI 0.68–0.72). We compared the differences in AUC values between PAPP-A and the model incorporating maternal factors, biochemical markers, and PAPP-A and found that the difference between them was statistically significant (Z= 9.983, P<0.001). Therefore, a lower serum PAPP-A in the first trimester is not a good

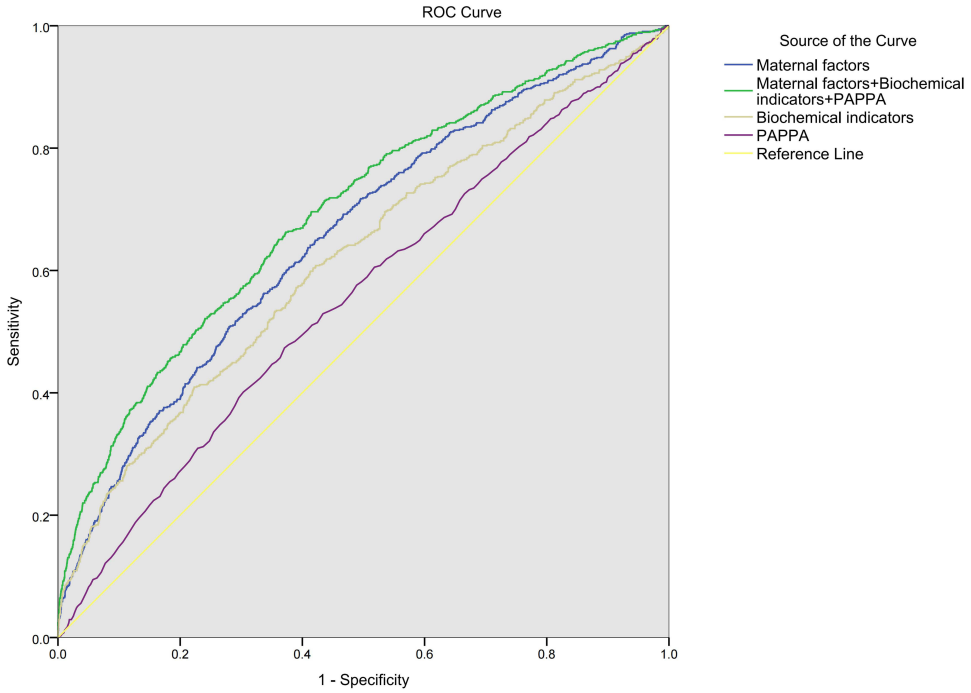

Figure 2 Receiver operating characteristic (ROC) curves for maternal factors, biochemical markers, PAPP-A, and a combination of maternal factors, biochemical markers, and PAPP-A for predicting GDM in the first trimester. The difference between PAPP-A and a combination of maternal factors, and biochemical markers was statistically significant (Z= 9.983, *P*<0.001).

independent predictor of GDM. Although the predictive value increases when combined with maternal factors and biochemical islet markers in a model, performance remains poor.

Insulin resistance is the key pathogenesis of GDM. With age, the function of the islet β-cells degrades, and insulin resistance increases. Insulin receptors in adipose membranes are relatively reduced, or their activity decreases. Previous studies[2,8] and the present study showed that maternal age, pre-gestational BMI, GWG before GDM diagnosis, family history of diabetes, and prior history of GDM were independent factors.

An elevated FPG level in the first trimester is associated with adverse pregnancy outcomes; an AUC of 0.63 (95% CI 0.61–0.65) has been reported to predict GDM in the first trimester.[12] Increased TG levels can cause insulin resistance and promote islet β cell apoptosis; insulin resistance closely influences lipid metabolism.[32] In the present study, elevated FPG, TG, TC, and LDL levels were independent factors for the occurrence of GDM. However, the predictive value of biochemical markers (FPG, TG, TC, and LDL) was weak. The AUCs were 0.58 (95% CI 0.56–0.60) for FPG, 0.58 (95%

Table 5 PAPP-A Performance as a Predictor for GDM

Cut-off Point, MOM	Sensitivity,% (95% CI)	Specificity,% (95% CI)	PLR (95% CI)	NLR (95% CI)	PPV,% (95% CI)	NPV,% (95% CI)
0.37	94.7 (93.1~96.3)	3.4 (2.9~4.0)	0.98 (0.96~1.00)	1.55 (1.10~2.18)	15.1 (14.1~16.2)	78.0 (72.0~84.0)
0.62	73.1 (69.9~76.2)	19.7 (18.5~20.9)	0.91 (0.87~0.95)	1.37 (1.20~1.56)	14.2 (13.1~15.3)	80.1 (77.6~82.6)
0.83*	52.7 (49.1 ~56.2)	37.1 (35.6~ 38.5)	0.84 (0.78~0.90)	1.28 (1.17~1.39)	13.2 (12.0~14.4)	81.1 (79.4~82.9)
0.88	48.9 (45.4~52.5)	41.6 (40.1~43.1)	0.84 (0.78~0.91)	1.23 (1.14~1.23)	13.2 (12.0~14.5)	81.7 (80.1~83.4)
1.13	30.8 (27.5~34.1)	64.5 (63.0 ~ 65.9)	0.87 (0.77~0.97)	1.07 (1.02~1.13)	13.6 (12.0~15.3)	83.7 (82.4~84.9)
1.38	15.1 (12.5~17.6)	81.1 (80.0~82.3)	0.80 (0.67~0.96)	1.05 (1.01~1.08)	12.7 (10.5~14.9)	84.0 (82.9~85.1)
1.64	7.9 (5.9~9.8)	90.8 (89.9~91.7)	0.85 (0.66~1.11)	1.02 (0.99~1.04)	13.4 (10.2~16.6)	84.4 (83.3~85.5)
1.89	3.2 (1.9~4.5)	96.0 (95.4~ 96.6)	0.81 (0.53~1.23)	1.01 (0.99~1.02)	12.8 (8.0~ 17.5)	84.5 (83.5~85.5)
2.15	1.6 (0.7~2.5)	98.4 (98.0~98.8)	0.99 (0.54~1.84)	1.00 (0.99~1.01)	15.4 (7.4~ 23.4)	84.6 (83.68~85.6)
2.41	0.3 (0.0~0.6)	99.3 (99.1~ 99.6)	0.41 (0.10~1.71)	1.00 (1.00~1.01)	6.9 (−2.3~16.1)	84.6 (0.83.5~85.6)

Notes: *Optimal cut-off point, which showed the highest combination of Sensitivity and Specificity.
Abbreviations: MOM, multiple of the median; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Table 6 FPG Performance as a Predictor for GDM

Cut-off Point, mmol/l	Sensitivity,% (95% CI)	Specificity,% (95% CI)	PLR (95% CI)	NLR (95% CI)	PPV,% (95% CI)	NPV,% (95% CI)
3.81	99.1 (98.4~99.8)	0.9 (0.6~1.2)	1.00 (0.99~1.01)	1.04 (0.47~2.32)	15.4 (14.4~16.4)	84.1 (73.3~94.9)
4.07	96.8 (95.5~98.1)	5.0 (4.3~5.7)	1.02 (1.00~1.03)	0.64 (0.42~0.97)	15.6 (14.6~16.7)	89.6 (85.6~93.5)
4.32	85.6 (83.1~88.1)	20.2 (19.0~21.5)	1.07 (1.04~1.11)	0.71 (0.59~0.86)	16.3 (15.2~17.5)	88.5 (86.5~90.6)
4.58	61.5 (58.0~64.9)	48.8 (47.3~50.3)	1.20 (1.13~1.28)	0.79 (0.72~0.87)	17.9 (16.4~19.4)	87.4 (86.1~88.8)
4.83	35.6 (32.2~39.0)	74.9 (73.6~76.3)	1.42 (1.27~1.59)	0.86 (0.81~0.91)	20.5 (18.3~22.7)	86.5 (85.4~87.6)
5.07*	19.9 (17.0~22.7)	91.4 (90.5~92.2)	2.30 (1.93~2.74)	0.88 (0.85~0.91)	29.5 (25.5~33.5)	86.2 (85.2~87.3)
5.08	19.1 (16.3~21.9)	91.7 (90.9~92.5)	2.30 (1.92~2.75)	0.88 (0.85~0.92)	29.5 (25.4~33.5)	86.2 (85.1~87.2)
5.34	9.2 (7.1~11.3)	97.8 (97.3~98.2)	4.17 (3.08~5.64)	0.93 (0.91~0.95)	43.1 (35.5~50.8)	85.5 (84.5~86.6)
5.60	5.3 (3.7~6.9)	99.4 (99.2~99.7)	9.16 (5.56~15.10)	0.95 (0.94~0.97)	62.5 (50.6~74.4)	85.2 (84.2~86.2)
5.98	2.9 (1.7~4.1)	99.7 (99.6~99.9)	10.99 (5.35~22.57)	0.97 (0.96~0.97)	66.7 (50.6~82.8)	85.0 (83.9~86.0)

Notes: *Optimal cut-off point, which showed the highest combination of Sensitivity and Specificity.
Abbreviations: MOM, multiple of the median; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Table 7 TG Performance as a Predictor for GDM

Cut-off Point, mmol/l	Sensitivity,% (95% CI)	Specificity,% (95% CI)	PLR (95% CI)	NLR (95% CI)	PPV,% (95% CI)	NPV,% (95% CI)
0.67	95.6 (94.1~97.1)	7.4 (6.6~8.2)	1.03 (1.01~1.05)	0.60 (0.42~0.85)	15.8 (14.7~16.9)	90.2 (87.0~93.4)
0.97	73.5 (70.3~76.6)	34.9 (33.4~36.3)	1.13 (1.08~1.18)	0.76 (0.67~0.86)	17.0 (15.7~18.3)	87.8 (86.3~89.4)
1.25*	49.1 (45.5~52.6)	62.7 (61.2~64.1)	1.31 (1.21~1.43)	0.81 (0.76~0.88)	19.3 (17.5~21.1)	87.1 (85.9~88.3)
1.27	46.8 (43.2~50.4)	64.3 (62.9~65.8)	1.31 (1.20~1.43)	0.83 (0.77~0.89)	19.3 (17.5~21.1)	86.9 (85.7~88.1)
1.58	27.5 (24.3~30.7)	82.7 (81.5~83.9)	1.59 (1.39~1.82)	0.88 (0.84~0.92)	22.4 (19.7~25.1)	86.2 (85.2~87.3)
1.88	15.3 (12.8~17.9)	91.0 (90.1~91.8)	1.70 (1.40~2.06)	0.93 (0.90~0.96)	23.6 (19.8~27.4)	85.5 (84.5~86.6)
2.18	10.0 (7.9~12.1)	94.7 (94.1~95.4)	1.90 (1.48~2.44)	0.95 (0.93~0.97)	25.7 (20.7~30.7)	85.3 (84.2~86.0)
2.49	5.2 (3.6~6.8)	97.2 (96.7~97.7)	1.88 (1.32~2.68)	0.98 (0.96~0.99)	25.5 (18.6~32.4)	84.9 (83.9~86.0)
2.81	3.1 (1.8~4.3)	98.7 (98.4~99.1)	2.39 (1.47~3.87)	0.98 (0.97~1.00)	30.3 (19.9~40.6)	84.8 (83.8~85.9)
3.43	1.3 (0.5~2.2)	99.4 (99.1~99.6)	2.11 (1.02~4.37)	0.99 (0.98~1.00)	27.8 (13.1~42.4)	84.7 (83.7~85.7)

Notes: *Optimal cut-off point, which showed the highest combination of Sensitivity and Specificity.
Abbreviations: MOM, multiple of the median; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Table 8 TC Performance as a Predictor for GDM

Cut-off Point, mmol/l	Sensitivity,% (95% CI)	Specificity,% (95% CI)	PLR (95% CI)	NLR (95% CI)	PPV,% (95% CI)	NPV,% (95% CI)
3.29	98.3 (97.3~99.2)	2.2 (1.7~2.6)	1.00 (0.99~1.02)	0.79 (0.45~1.41)	15.5 (14.4~16.5)	87.4 (81.0~93.8)
3.66	90.0 (87.9~92.1)	10.4 (9.5~11.4)	1.00 (0.98~1.03)	0.96 (0.76~1.21)	15.5 (14.4~16.5)	85.1 (82.0~88.3)
4.13	74.1 (71.0~77.3)	28.0 (26.7~29.4)	1.03 (0.98~1.08)	0.92 (0.81~1.05)	15.8 (14.6~17.0)	85.6 (83.8~87.5)
4.60	53.1 (49.5~56.6)	52.4 (50.9~53.9)	1.12 (1.04~1.20)	0.90 (0.83~0.97)	16.9 (15.4~18.4)	86.0 (84.6~87.3)
4.71*	49.6 (46.0~53.2)	58.2 (56.7~59.7)	1.19 (1.09~1.29)	0.87 (0.80~0.93)	17.7 (16.1~19.4)	86.4 (85.1~87.7)
5.07	34.5 (31.1~37.9)	72.0 (70.6~73.4)	1.23 (1.10~1.38)	0.91 (0.86~0.96)	18.3 (16.3~20.3)	85.8 (84.6~87.0)
5.54	15.9 (13.3~18.5)	85.5 (84.4~86.5)	1.09 (0.91~1.31)	0.98 (0.95~1.02)	16.6 (13.9~19.3)	84.8 (83.7~85.9)
6.01	8.5 (6.5~10.5)	93.1 (92.3~93.8)	1.23 (0.95~1.59)	0.98 (0.96~1.01)	18.3 (14.2~22.3)	84.8 (83.8~85.9)
6.49	3.5 (2.2~4.8)	96.9 (96.4~97.4)	1.13 (0.74~1.70)	1.00 (0.98~1.01)	17.0 (11.0~22.9)	84.7 (83.6~85.7)
7.12	1.3 (0.5~2.2)	98.9 (98.6~99.2)	1.20 (0.61~2.36)	1.00 (0.99~1.01)	17.9 (27.9~84.6)	84.6 (83.6~85.7)

Notes: *Optimal cut-off point, which showed the highest combination of Sensitivity and Specificity.
Abbreviations: MOM, multiple of the median; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

CI 0.56–0.60) for TG, 0.53 (95% CI 0.51–0.56) for TC and 0.55 (95% CI 0.53–0.57) for LDL respectively. The AUC of combined FPG, TG, TC, and LDL was 0.62 (95% CI 0.60 0.64). The optimal cut-off point for FPG was 5.07 mmol/l with sensitivity (19.9%) and specificity (91.4%), TG was 1.25 mmol/l with sensitivity (49.1%) and specificity (62.7%), TC

Table 9 LDL Performance as a Predictor for GDM

Cut-off Point, mmol/l	Sensitivity,% (95% CI)	Specificity,% (95% CI)	PLR (95% CI)	NLR (95% CI)	PPV,% (95% CI)	NPV,% (95% CI)
1.21	98.7 (97.8~99.5)	1.3 (1.0~1.7)	1.00 (0.99~1.01)	1.02 (0.52~1.99)	15.4 (14.4~16.4)	84.4 (75.5~93.3)
1.58	93.2 (91.4~95.0)	7.7 (6.9~8.5)	1.01 (0.99~1.03)	0.88 (0.66~1.17)	15.5 (14.5~16.6)	86.2 (82.7~93.2)
1.95	76.3 (73.2~79.3)	25.4 (24.1~26.7)	1.02 (0.98~1.07)	0.93 (0.81~1.07)	15.7 (14.5~16.9)	85.5 (83.5~87.4)
2.32	56.5 (53.0~60.1)	50.9 (49.4~52.5)	1.15 (1.08~1.24)	0.85 (0.78~0.93)	17.3 (15.8~18.8)	86.6 (85.2~87.9)
2.45*	50.4 (46.8~54.0)	59.3 (57.8~60.8)	1.24 (1.14~1.34)	0.84 (0.78~0.90)	18.4 (16.7~20.0)	86.8 (85.5~88.0)
2.68	33.9 (30.5~37.3)	73.0 (71.6~74.4)	1.25 (1.12~1.40)	0.91 (0.86~0.96)	18.6 (16.5~20.6)	85.8 (84.7~87.0)
3.04	20.4 (17.5~23.3)	86.3 (85.3~87.4)	1.49 (1.27~1.75)	0.92 (0.89~0.96)	21.4 (18.4~24.4)	85.6 (84.6~86.7)
3.41	8.9 (6.9~11.0)	93.9 (93.2~94.6)	1.46 (1.13~1.89)	0.97 (0.95~0.99)	21.0 (16.5~25.5)	85.0 (84.0~86.0)
3.78	4.0 (2.6~5.4)	97.0 (96.5~97.6)	1.35 (0.91~2.00)	0.99 (0.97~1.00)	19.7 (13.4~26.1)	84.7 (83.7~85.8)
4.28	1.5 (0.6~2.3)	98.9 (98.6~99.2)	1.34 (0.70~2.59)	1.00 (0.99~1.00)	19.6 (9.2~30.0)	84.7 (83.6~85.7)

Notes: *Optimal cut-off point, which showed the highest combination of Sensitivity and Specificity.
Abbreviations: MOM, multiple of the median; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

was 4.71 mmol/l with sensitivity (49.6%) and specificity (58.2%), LDL was 2.45 mmol/l with sensitivity (50.46%) and specificity (59.3%), respectively.

Although many studies have evaluated the association between PAPP-A in the first trimester and the development of GDM, the results remain controversial. A meta-analysis by Talasaz et al[21] of 17 publications suggested that a low PAPP-A level in early pregnancy was associated with GDM; the sensitivity and specificity for predicting GDM were 55% (53–58%) and 90% (89–90%), respectively, with an AUC (0.7) indicating low precision. The present results are similar to those of Talasaz et al in that the PAPP-A level in the GDM group was much lower than in the non-GDM group. This study found that a low serum PAPP-A in the first trimester was associated with the occurrence of GDM, but the AUC was only 0.56 (95% CI: 0.53–0.58), and the optimal cut-off point was 0.83 MOM with sensitivity (52.7%) and specificity (37.1%), similar to Yanachkova's findings (AUC = 0.57, 95% CI 0.55–0.61).[28] Ren Z et al[27] found that a lower level of serum PAPP-A was an independent factor affecting the occurrence of GDM and had a certain value in the diagnosis of GDM with an AUC of 0.861. In the meta-analysis of 13 studies (9 conducted in Europe, 2 in Australia, and 2 in China) by Donovan et al,[22] women with diagnosed GDM had lower levels of PAPP-A in the first trimester compared to women who remained normoglycemic. The effect was slightly less among the studies conducted in Asia than in Europe or Australia. Browne et al[33] found that women of sub-Saharan African descent had higher levels of PAPP-A than Caucasian or Afro-Caribbean women, with serum samples taken between 56 and 97 days of pregnancy. This finding called into question the predictive value of PAPP-A for GDM.

The reasons why low levels of PAPP-A are associated with the occurrence of GDM remain undetermined. Yan et al[34] showed that PAPP-A increased the bioavailability of insulin growth factor-1 (IGF-1) by dissociating it from insulin-like growth factor binding proteins. Pregnant women with low levels of PAPP-A have low IGF-1, which can lead to hyperinsulinemia, resulting in GDM. Other reports suggested no differences in PAPP-A levels in women with or without GDM in the first trimester of pregnancy.[25,26] Rather, the differences may be related to ethnicity, research design, diagnostic criteria for GDM, or the study's statistical power.

It is still debatable whether the model incorporating PAPP-A with maternal factors and biochemical markers has a more predictive value than the model with the latter two alone. In the present study, the AUC of PAPP-A was 0.56. The AUC of the model incorporating maternal factors, biochemical markers, and PAPP-A was 0.70. We compared the difference in AUC values between PAPP-A and the model incorporating maternal factors, biochemical markers, and PAPP-A using the Delong test[30] and found that the difference between them was statistically significant ($Z= 9.983$, $P<0.001$). Other researchers have evaluated various other readily accessible parameters. Sweeting et al[35] showed that a model that integrated the PAPP-A level in the first trimester and the uterine artery pulsatility index (UtA-PI) with maternal clinical characteristics had a higher predictive value than the model with maternal characteristics alone. The model performed best overall in women with early GDM (<24 weeks) [AUC 0.96 (95% CI 0.94–0.98)]. Syngelaki et al[29] found that, for predicting GDM, the AUCs for maternal factors, PAPP-A, placental growth factor, or their combinations were not significantly different from maternal factors alone. Xiao et al[36] reported

an AUC of 0.533 for PAPP-A and an AUC of 0.684 for maternal clinical characteristics, while PAPP-A combined with maternal clinical characteristics produced an AUC of 0.686.

In a study of nulliparous women, Snyder et al[37] showed first-trimester PAPP-A, second-trimester unconjugated estriol (uE3), and dimeric inhibin A (INH) had limited clinical utility for predicting GDM risk. Tenenbaum-Gavish et al[38] developed a new first-trimester prediction model for gestational diabetes mellitus (GDM) using obesity, placental and inflammatory biomarkers. In obese women, the combination of high BMI, insulin, sCD163, and TNFα yielded an AUC of 0.95, with an 89% detection rate at a 10% false positive rate; In non-obese women, sCD163, TNFα, PP13, and PAPP-A produced an AUC of 0.94, with an 83% detection rate at a 10% false positive rate. The authors concluded that their new model for first-trimester prediction of the risk of developing GDM warrants further validation.

The present study had the following strengths. First, we included a comprehensive range of maternal factors and biochemical markers in the pregnancy. Second, it has supplemented the paucity of data on PAPP-A combined with other parameters to predict GDM in Asia, especially southern China. Finally, this was a large retrospective, case-control, observational study. Although our study has many strengths, we also acknowledge its limitations. The limitations include its retrospective nature and single-center data source, which could limit its widespread application and relevance. Because our data source was the medical records, inaccurate reporting of demographic and clinical variables wasted possible. In addition, this study only examined patients affected by GDM and neglected women with pregestational diabetes mellitus. Further prospective studies may confirm our findings.

Conclusion

A Low serum PAPP-A level in the first trimester is an independent risk factor for developing GDM later in pregnancy. However, it is not a good independent predictor. Although its predictive value increases when combined with maternal factors and biochemical markers, the performance remains poor.

Data Sharing Statement

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was carried out according to the principles of the Declaration of Helsinki and approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-Sen University (serial number: [2021]02–266-01). The ethics committee of the Third Affiliated Hospital of Sun Yat-Sen University approved the exemption from informed consent. This retrospective, case-controlled, observational study did not jeopardize the confidentiality and autonomy of any study participant.

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Author Contributions

All authors contributed significantly to this work in the conception, study design, execution, acquisition of data, analysis, and interpretation, individually or all these areas. All authors participated in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the manuscript has been submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report that there are no conflicts of interest in this work.

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