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Gestational diabetes mellitus and first trimester pregnancy-associated plasma protein A: A case–control study in a Chinese population

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ABSTRACT

Aims/Introduction: To investigate the relationship between pregnancy-associated plasma protein A (PAPP-A) and gestational diabetes mellitus (GDM), and to determine whether PAPP-A has improved value for predicting GDM in a Chinese population.

Materials and Methods: Clinical data for 599 GDM patients and 986 unaffected pregnant women undergoing both antenatal examinations and delivery were retrospectively analyzed. First-trimester serum PAPP-A levels were compared between the groups. Binary logistic regression analysis was used to explore the risk factors for GDM, and the area under the receiver operating characteristic curve was used to determine the value of PAPP-A for predicting GDM.

Results: GDM-affected and unaffected pregnant women were significantly different in terms of age ($P < 0.001$), BMI ($P < 0.001$), family history of diabetes ($P = 0.002$), α-thalassemia trait ($P < 0.01$), parity ($P < 0.001$), conception methods ($P < 0.001$), gestational weeks at the time of labor ($P < 0.001$) and corrected PAPP-A multiples of the median values ($P < 0.001$). Binary logistic regression analysis showed that PAPP-A levels were negatively related to the subsequent development of GDM (odds ratio 0.798, 95% confidence interval 0.647–0.984). The area under the receiver operating characteristic curve for maternal factors was 0.684 (95% CI: 0.657–0.711), and did not significantly differ from that for the combination of maternal factors and serum PAPP-A levels, which was 0.686 (95% CI: 0.660–0.713; $\chi^2 = 0.625$, $P = 0.429$).

Conclusions: Serum PAPP-A was an independent factor for the development of GDM in pregnant Chinese women. Serum-PAPP-A does not have improved value with respect to predicting GDM when combined with other maternal factors.

INTRODUCTION

China has a large diabetes burden. In 2013, one-quarter of the people with diabetes worldwide were Chinese, and 11.6% of adults who lived in China had diabetes[1]. The prevalence of diabetes in China has increased substantially in recent years, as more than 100 million people are currently estimated to be affected by the disease[2]. The prevalence of gestational diabetes mellitus (GDM), defined as 'any degree of glucose intolerance associated with the onset of pregnancy or glucose intolerance that is first recognized during pregnancy'[3], has also increased markedly in the region[4]. The cumulative incidence of type 2 diabetes in women with previous GDM increased from 2.6% at 6 weeks after delivery to 70% at 28 years after delivery[4]. Furthermore, the rates of type 2 diabetes in the offspring of GDM-affected mothers have increased markedly[5]. GDM is likely to be a significant factor contributing to the epidemic of diabetes in China, which means that high GDM rates might reflect a high prevalence of diabetes in the general population. Unfortunately, GDM cannot be diagnosed until late in the second trimester, and there is no valid predictor of GDM. Clarifying whether any routine first-trimester biochemical markers are altered in pregnant women who subsequently develop GDM might allow early detection of at-risk women, and facilitate subsequent interventions to reduce the morbidities associated with GDM[6].

China is a developing country, wherein some districts remain low-resource settings. In light of this fact, a biomarker that is

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not only effective in screening for GDM, but is also economical, would be optimal. Therefore, we focused on serum pregnancy-associated plasma protein A (PAPP-A), which is a routine indicator used for Down syndrome (DS) screening. The added utility of this biomarker with respect to predicting GDM came at no extra cost.

PAPP-A is produced by the syncytiotrophoblast, and is maintained at high concentrations in the circulation and placenta during pregnancy. PAPP-A is widely applied during the first trimester, along with free β-human chorionic gonadotropin (fβ-hCG), to assess the risk of DS. PAPP-A and fβ-hCG are affected by maternal and pregnancy factors, including maternal age, weight, ethnicity, smoking status and conception methods. All of these factors can be used to calculate multiples of the median (MoM). Previous studies have suggested that if pregnant women had a decreased risk of DS with low serum PAPP-A levels during the first trimester, they would be at higher risk for developing pregnancy complications or experiencing adverse outcomes[7], such as preterm delivery, intrauterine growth restriction and pre-eclampsia[8–10]. These findings might show that first trimester PAPP-A levels are a predictive marker for GDM.

Some studies have reported that PAPP-A levels were impaired among women who subsequently developed GDM[6,11–15] (Table 1). Five studies determined that their median or mean PAPP-A MoM values were 0.9, 0.7, 0.949, 0.91 and 1.11. Another study divided GDM into early-onset and late-onset groups according to whether the time of diagnosis was before or after 22 gestational weeks. The median PAPP-A MoM was 0.94 in the early-onset GDM group and 0.79 in the late-onset GDM group. Other studies showed that there were no differences in PAPP-A levels between GDM-affected and unaffected pregnancies[16–18]. The median and mean PAPP-A MoM values in these studies were 0.94, 1.17 and 0.97, respectively. Six of these previous studies also discovered the existence of a relationship between fβ-hCG MoM values and GDM. Only one of these studies found positive results. The median fβ-hCG MoM values were 0.93. However, Caucasian patients were the main participants in these previous studies, which failed to consider Asian populations, especially Chinese populations, and GDM is associated with ethnicity. Only one study focused on a Chinese population, but using old World Health Organization (WHO) 1999 criteria[19] published in 2016[18]. Furthermore, as new criteria for the diagnosis of GDM were proposed in 2013, we would like to know whether the use of new diagnostic standards would affect our results regarding the diagnosis of GDM.

The aim of the present study was to assess whether serum PAPP-A levels were altered at 11–13^{+6} weeks of gestation in Chinese women who eventually developed GDM, and to determine whether this biomarker can predict GDM or show improved value for predicting GDM when combined with maternal factors.

Table 1 | First trimester maternal serum pregnancy-associated plasma protein A and free β-human chorionic gonadotropin levels in women with/without gestational diabetes mellitus

Previous studies	*n*		PAPP-A MoM		fβ-hCG MoM	
	GDM	Controls	GDM	Controls	GDM	Controls
Lovati *et al.*[6] (2013)	307	366	0.9 ± 0.6*	1.3 ± 0.6	1 (0.7–1.6)	1.05 (0.7–1.6)
Beneventi *et al.*[11] (2011)	228	228	0.7 (0.5–1.2)*	1.2 (0.8–1.6)	0.9 (0.6–1.6)	1 (0.7–1.5)
Wells *et al.*[13] (2015)	364	1,282	Late: 0.94 (0.63–1.31)* Early: 0.79 (0.51–1.28)*	1.00 (0.68–1.40)	–	–
Syngelaki *et al.*[12] (2015)	787	30,438	0.949 (0.913–0.987)*	1.000 (0.994–1.006)	–	–
Savvidou *et al.*[17] (2012)	779	41,007	0.94 (0.65–1.39)	1.00 (0.68–1.42)	0.95 (0.64–1.39)	1.00 (0.68–1.52)
Husslein *et al.*[16] (2012)	72	216	1.17 ± 0.71	1.13 ± 0.58	1.13 ± 0.73	1.15 ± 0.64
Spencer *et al*[15] (2013)	870	6,559	0.91*	1.00	0.93	1.00
Beneventi *et al.*[14] (2014)	112	112	1.06 ± 0.59*	1.22 ± 0.64	–	–
Cheuk *et al.*[18] (2016)	169	351	0.97 (0.65–0.32)	0.99 (0.67–1.44)	1.05 (0.73–1.64)	1.02 (0.71–1.55)

Values are expressed as the mean ± standard deviation or as medians (interquartile ranges). *$P < 0.05$ compared with the control group. fβ-hCG, free β-human chorionic gonadotropin; MoM, multiple of the median; PPAP-A, pregnancy-associated plasma protein A.

METHODS

Study population and Eligibility criteria

This was a case–control study of singleton pregnant women who underwent both antenatal examinations and delivery at the Department of Obstetrics and Gynecology of the Maternal and Child Healthcare Hospital of Shenzhen, China, during the period of July 2014 to December 2015. The antenatal examinations included screenings for DS by ultrasound and biochemistry markers (PAPP-A and fβ-hCG) during the first trimester, and screenings for GDM during the late second trimester.

Women who met the following criteria were excluded from the study: (i) women with multiple gestations; (ii) women with pregestational diseases (diabetes, hypertension, nephropathy and thyroid dysfunction); (iii) women with fetuses with other genetic or congenital malformations; and (iv) women who gave birth at <30 gestational weeks.

During this period, 599 enrolled pregnant women were diagnosed with GDM, and 986 euglycemic women were randomly selected as the control group.

The diagnosis of GDM was confirmed when any glucose values exceeded the standard cut-off levels (fasting, 5.1 mmol/L; 1 h, 10.0 mmol/L; and 2 h, 8.50 mmol/L), which were based on a 2-h 75-g oral glucose tolerance test[20]. All GDM patients were treated with lifestyle modification (dietary changes and exercise) or lifestyle modification combined with insulin.

Written consent was obtained before data utilization according to local ethics committee requirements.

Data collection

Data regarding maternal characteristics were collected at 11–13^{+6} weeks gestation using questionnaires administered at the time of the combined screening for DS. We recorded the following data: maternal age, prepregnancy body mass index (BMI), ethnicity, smoking status, parity, mode of conception, family history of diabetes and hypertension, and maternal serum PAPP-A and fβ-hCG. Gestational weeks were based on the last menstrual period, and were confirmed by ultrasound results. Serum PAPP-A and fβ-hCG levels were measured by the Certified Hospital Laboratory Department (Maternal and Child Healthcare Hospital of Shenzhen, China) using a DELFIA Xpress system (PerkinElmer Life, Waltham, Massachusetts, USA). All samples were tested within 48 h after blood sampling. MoM values and DS risks were calculated using LIFE CYCLE software (PerkinElmer, Turku, Finland). Data on maternal and neonatal outcomes were collected at the time of delivery. All of these data were entered into an electronic database.

Statistical analysis

Means and standard deviations were used to describe normally distributed variables, and medians and interquartile ranges were used to describe non-normally distributed variables. Frequencies were used to describe categorical variables, *t*-tests and Mann–Whitney *U*-tests were used for in-group comparisons of quantitative variables, and Pearson's χ^2-test was used for comparisons of categorical variables. Binary logistic regression with forced entry was used to examine risk factors in multivariate models. The probabilities for stepwise entry and removal were 0.10 and 0.15, respectively. The area under the receiver operating characteristic (AUC-ROC) curve was used to test the value of PAPP-A for predicting GDM.

AUC-ROCs were compared using SigmaPlot software (version 12.5; Systat, San Jose, California, USA)[21]. Other statistical analyses were carried out using Spss software (version 20.0; IBM, Armonk, New York, USA). All tests were two-tailed, and *P*-values <0.05 were regarded as statistically significant.

RESULTS

Study population

Information regarding maternal and pregnancy characteristics is shown in Table 2. All the women were non-smokers. Women who developed GDM tended to be older, have higher BMIs and give birth earlier than women in the control group ($P < 0.001$). Furthermore, the proportions of patients with a family history of diabetes ($P < 0.01$) and α-thalassemia trait ($P < 0.01$), as well as the proportions of patients who were parous ($P < 0.001$) and used assisted reproductive technology ($P < 0.001$), were higher in the GDM group than in the control group. There was no significant difference in nationality, family history of hypertension, β-thalassemia trait, neonatal sex or neonatal birthweight between the two groups ($P > 0.05$). Just 20 women in the GDM group were treated with dietary modification combined with insulin, whereas most women could control their serum glucose levels with dietary modification and exercise.

Serum PAPP-A MoM values and fβ-hCG MoM values were 0.88 (interquartile range [IQR] 0.60–1.28) and 1.01 (IQR 0.69–1.58), respectively, during the first trimester in women who developed GDM, and 0.97 (IQR 0.67–1.37) and 1.06 (IQR 0.73–1.62), respectively, during the first trimester in women in the control group (Table 3). In the present study, first trimester serum PAPP-A levels were significantly lower in women who subsequently developed GDM than in women in the control group ($P < 0.001$). We also noticed that fβ-hCG MoM values were decreased in the GDM group compared with their corresponding values in the control group, but the difference between the two groups did not achieve statistical significance ($P > 0.05$).

Risk factors for GDM development

The only variables that were significant in the binary logistic regression analysis are outlined at Table 4 ($P < 0.05$). Older maternal age, a higher prepregnancy BMI, *in vitro* fertilization and embryo transfer, α-thalassemia trait, and a lower serum PAPP-A MoM value were independent risk factors for GDM development. No other factors were significantly associated with GDM development.

Table 2 | Maternal and pregnancy characteristics of the study population

Variable	GDM group (n = 599)	Control group (n = 986)	P-value
Median Maternal, years (IQR)	32 (29–34)	29 (27–32)	<0.001*
Nationality			
Han, n (%)	588 (98.2%)	969 (98.3%)	0.869
Minority, n (%)	11 (1.8%)	17 (1.7%)	
Median maternal prepregnancy BMI, kg/m^2 (IQR)	20.83 (19.23–23.03)	19.72 (18.43–21.40)	<0.001*
Maternal family history of diabetes, n (%)	45 (7.5%)	75 (3.9%)	0.002*
Maternal family history of hypertension, n (%)	75 (12.5%)	95 (9.6%)	0.072
α-Thalassemia, n (%)	14 (2.3%)	7 (0.7%)	0.006*
β-Thalassemia, n (%)	6 (1.0%)	11 (1.1%)	0.831
Parity			
Nulliparous, n (%)	382 (63.8%)	745 (75.6%)	<0.001*
Parous, n (%)	217 (36.2%)	241 (24.4%)	
Conception			
Spontaneous, n (%)	567 (94.7%)	976 (99%)	<0.001*
Ovulation induction, n (%)	5 (0.8%)	2 (0.2%)	
In vitro fertilization, n (%)	27 (4.5%)	8 (0.8%)	
Median gestational age at delivery, days (IQR)	276 (272–280)	278 (272–283)	<0.001*
Sex of newborn			
Male, n (%)	291 (48.6%)	498 (50.5%)	0.457
Female, n (%)	308 (51.4%)	488 (49.5%)	
Birthweight, g (mean ± SD)	3,306.53 ± 433.85	3,315.03 ± 370.82	0.690

*P < 0.05 compared with the control group. BMI, body mass index; GDM, gestational diabetes mellitus; IQR, interquartile range; SD, standard deviation.

Table 3 | Maternal serum pregnancy-associated plasma protein A multiple of the median and free β-human chorionic gonadotropin multiple of the median values of the study population

Marker	GDM group (n = 599)	Control group (n = 986)	P-value
Median gestational age at sampling, days (IQR)	89 (86–92)	89 (85–92)	0.447
Median PAPP-A MoM (IQR)	0.88 (0.60–1.28)	0.97 (0.67–1.37)	<0.001*
Median fβ-hCG MoM (IQR)	1.01 (0.69–1.58)	1.06 (0.73–1.62)	0.133

*P < 0.05 compared with the control group. fβ-hCG, free β-human chorionic gonadotropin; GDM, gestational diabetes mellitus; IQR, interquartile range; MoM, multiple of the median; PPAP-A, pregnancy-associated plasma protein A.

Table 4 | Binary logistic regression analysis of the risk factors associated with gestational diabetes mellitus

Variable	OR	95% CI	Coefficient	SE	P-value
Maternal age	1.108	1.074–1.143	0.102	0.016	<0.001
Maternal prepregnancy BMI	1.127	1.097–1.194	0.135	0.022	<0.001
Conception					
Spontaneous, n (%)	Reference				
IVE-ET, n (%)	4.151	1.822–9.459	1.423	0.420	0.001
α-Thalassemia	3.253	1.260–8.398	1.180	0.484	0.015
PAPP-A MoM	0.798	0.647–0.984	–0.225	0.107	0.035

BMI, body mass index; CI, confidence interval; IVF-ET, *in vitro* fertilization and embryo transfer; MoM, multiple of the median; PPAP-A, pregnancy-associated plasma protein A; SE, standard error.

GDM screening performance

The AUC-ROCs were 0.533 (95% confidence interval [CI] 0.524–0.583) for serum PAPP-A MoM values, 0.684 (95% CI: 0.657–0.711) for maternal factors and 0.686 (95% CI: 0.660–0.713) for maternal factors combined with serum PAPP-A MoM values. Adding PAPP-A MoM values to maternal factors

did not improve the performance of maternal factors with respect to screening for GDM ($\chi^2 = 0.625$, $P = 0.429$).

DISCUSSION

In the present study, we showed that first-trimester serum PAPP-A MoM values were decreased in pregnant women who subsequently developed GDM, and that low PAPP-A levels were an independent risk factor for GDM development. However, the power of maternal factors to predict GDM was not improved by the addition of PAPP-A.

Nine previous studies examined the relationship between first-trimester PAPP-A levels and GDM. Six of those studies reported that serum PAPP-A levels were lower in GDM women than in women with unaffected pregnancies. Lovati *et al.*,[6] Syngelaki *et al.*,[12] Beneventi *et al.*,[11] Spencer *et al.*[15] and Beneventi *et al.*[14] found that serum PAPP-A levels were decreased by 5.1–30.8% among patients who eventually developed GDM. Wells *et al.*[13] innovatively divided GDM patients into the following two separate groups: an early-onset GDM group (diagnosed <22 weeks) and a late-onset GDM group (diagnosed ≥22 weeks). These authors found that the PAPP-A MoM value was 22.6% lower in early-onset GDM pregnancies and 8.6% lower in late-onset GDM pregnancies than in normal pregnancies. The present study found that PAPP-A levels were reduced by 9% in GDM pregnancies compared with normal pregnancies, a finding that was consistent with those of the aforementioned four previous research studies. Lower first trimester PAPP-A levels in pregnant women who eventually developed GDM might be reflective of an initial stage of glucose intolerance that is already present at the beginning of pregnancy[11]. The relationship between decreased PAPP-A levels and the pathogenesis of GDM is under investigation. There is evidence that PAPP-A can increase the bioavailability of insulin growth factor-1 by dissociating from insulin growth factor-binding proteins[22]. Low PAPP-A levels can induce low insulin growth factor 1 levels, which can lead to hyperinsulinemia and abnormal glucose clearance, and might be negatively related to insulin resistance[23]. These findings could explain why GDM patients have reduced PAPP-A levels during the first trimester. However, Savvidou *et al.*,[17] Husslein *et al.*[16] and Cheuk *et al.*[18] found that serum PAPP-A MoM levels were not significantly altered in GDM.

Just three of these nine previous studies examined whether serum PAPP-A levels could be a predictor of GDM during the first trimester, and their results contrast. Syngelaki *et al.*[12] found that PAPP-A levels are not useful for screening for GDM. Furthermore, the AUC-ROC for maternal factors combined with PAPP-A MoM values (0.8409) showed that this combination did not have improved value for predicting GDM compared with maternal factors only (0.8409). In contrast, Lovati *et al.*[6] found that the AUC-ROC was 0.70 (95% CI: 0.60–0.74) for adjusted scores including PAPP-A levels, whereas the AUC-ROC was 0.60 (95% CI: 0.56–0.64) for clinical risk factors only, indicating that PAPP-A levels might be a potential biomarker for screening for GDM. Spencer *et al.*[15] found PAPP-A was a weak, but significant, predictor of GDM with AUC-ROC of 0.55 (95% CI: 0.53–0.57). The present study showed that serum PAPP-A levels could not improve the predictive value of maternal factors when combined with maternal factors.

A potential explanation for the differences in the results of the various aforementioned studies could be the severity of GDM in the study populations of these investigations. The group with GDM who were treated with insulin in the Spencer *et al.*[15] and in Beneventi *et al.*[14] studies were 12 and 23.2%, respectively. Just two (1.2%) women with GDM in the study by Cheuk *et al.*[18] required insulin treatment. Wells *et al.*[13] assessed 63 early GDM and 301 late GDM patients, and noted that some early GDM patients might have had undiagnosed type 2 diabetes. The research population of the study by Syngelaki *et al.*[12] was divided into GDM on diet control (36.7%), GDM on metformin (18.2%) and GDM on insulin (46.1%) based on GDM severity[12]. PAPP-A levels were different among those groups. They were lowest in the GDM on insulin group and highest in the GDM on diet control group. Husslein *et al.*[16] studied GDM-affected patients who were treated with insulin only. The present study included 20 patients (3.3%) who required insulin treatment. The other three studies did not mention GDM patient subgroups. These findings show that the severity of GDM was different in those studies, which could have led to variations in their results.

Another possible explanation for the aforementioned diverse outcomes might be differences in the diagnostic criteria used in the indicated studies. GDM was diagnosed in these previous studies using different criteria. The guidelines from the 1999 WHO and 2001 American Diabetes Association were the main diagnostic criteria before 2013. More recently, the Hyperglycemia and Adverse Pregnancy Outcome study reported that even less severe maternal hyperglycemia could lead to adverse pregnancy outcomes[24]. On the basis of these findings, a new criterion was proposed by the International Association of Diabetes and Pregnancy Study Groups[20], and was subsequently adopted by the WHO[25] and American Diabetes Association in 2013. Although three of these nine previous studies were published after 2015, data of two studies were collected before 2013, and the data of the other study were used by WHO 1999[19] as a diagnostic criterion. Only our study used the new International Association of Diabetes and Pregnancy Study Groups criteria[20] to diagnose GDM.

Furthermore, Caucasians were the main participants in these previous studies. Two of the studies also involved some Africans and a few southern Asians. Only one study focused on a Chinese population, but using old WHO 1999 criteria[19] published in 2016[18]. In the present study, a Chinese population was the only population that we evaluated. Thus, differences in the populations with GDM, which is partly related to ethnicity, might be a reason for the differences in the results of the aforementioned studies.

In addition, the present study did not find a significant difference in fβ-hCG MoM values between GDM-affected patients and unaffected pregnant women, a finding similar to those of previous studies[6,11,16–18]. Only Spencer *et al.*[15] found fβ-hCG MoM was a weak, but significant, predictor of GDM with AUC-ROC of 0.54 (95% CI: 0.52–0.56; Table 1).

There were two unexpected discoveries in the present study. One was that prepregnancy BMI values in women with gestational diabetes in this population were still lower than those in Western populations, although they were higher than those in the control group. One possible explanation for this finding was that the increased visceral adiposity of the Chinese population, which is caused by the use of a special dietary structure in China, could carry an increased risk of diabetes and glucose abnormalities[26]. The other finding was that pregnant women with the α-thalassemia trait were more likely to develop to GDM than other pregnant women. Lao *et al.*[27] investigated 3,320 pregnant women in Hong Kong in a case–control study. They found that the incidence of GDM in women with the α-thalassemia trait was significantly higher (62.0%) than the incidence of GDM in the control group, and that the risk of GDM in the former group was fourfold higher than the risk of GDM in the control group. Increased iron stores in women with the α-thalassemia trait might contribute to the development of GDM[27,28]. However, we did not observe the same results in pregnant women with the β-thalassemia trait. More research is required to establish these relationships.

The strength of the present study is that it is the first to discover the power of first trimester serum PAPP-A values to predict GDM in Chinese women who are pregnant by using new International Association of Diabetes and Pregnancy Study Groups diagnostic criteria[20]. Furthermore, we examined 1,585 singleton pregnant women (599 GDM-affected patients and 986 unaffected women) who had routine antenatal care before delivery. All the women underwent fasting glucose level testing as a routine screening test for pregestational diabetes mellitus (PGDM) at their initial prenatal visit to eliminate the diagnosis of pre-pregnancy diabetes[29].

It should be noted that this study examined only GDM-affected patients and neglected women with pregestational diabetes mellitus. In addition, as the present study was a case–control study, its interpretation of predictive value is of limited relevance. This limitation notwithstanding, the present study clearly showed the relationship between first trimester serum PAPP-A levels and GDM. Additional prospective studies are underway to certify these results.

Low serum PAPP-A was an independent factor for GDM development during the first trimester in a Chinese population. However, serum PAPP-A could not improve the performance of maternal factors with respect to the early prediction of GDM when combined with these factors.

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DISCLOSURE

The authors declare no conflict of interest.

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