Association between pregnancy-associated plasma protein-A levels in the first trimester and gestational diabetes mellitus in Chinese women

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A B S T R A C T

Introduction: Several studies have shown that women with pre-existing diabetes mellitus have significantly lower pregnancy–associated plasma protein-A levels than those without. This study aimed to evaluate whether first-trimester pregnancy–associated plasma protein-A multiple of median is associated with gestational diabetes mellitus in Chinese pregnant women.

Methods: This prospectively collected case series was conducted in a regional hospital in Hong Kong. All consecutive Chinese women with a singleton pregnancy who attended the hospital for their first antenatal visit (before 14 weeks' gestation) from April to July 2014 were included. Pregnancy-associated plasma protein-A multiple of median was compared between the gestational diabetic (especially for early-onset gestational diabetes) and non-diabetic groups. The correlation between pregnancy-associated plasma protein-A level and glycosylated haemoglobin level in women with gestational diabetes was also examined.

Results: Of the 520 women recruited, gestational diabetes was diagnosed in 169 (32.5%). Among them, 43 (25.4%) had an early diagnosis, and 167 (98.8%) with the disease were managed by diet alone. The gestational diabetic group did not differ significantly to the non-diabetic group in pregnancy-associated plasma protein-A (0.97 vs 0.99, P=0.40) or free β-human chorionic gonadotrophin multiple of median (1.05 vs 1.02, P=0.29). Compared with the non-gestational diabetic group, women with early diagnosis of gestational diabetes had a non-significant reduction in pregnancy-associated plasma protein-A multiple of median (median, interquartile range: 0.86, 0.57-1.23 vs 0.99, 0.67-1.44; P=0.11). Pregnancy-associated plasma protein-A and glycosylated haemoglobin levels were not correlated in women with gestational diabetes ($r=0.027$; P=0.74).

Conclusions: Chinese women with non–insulin-dependent gestational diabetes did not exhibit significant changes to pregnancy-associated plasma protein-A multiple of median nor a correlation between pregnancy-associated plasma protein-A with glycosylated haemoglobin levels. Pregnancy-associated plasma protein-A multiple of median was not predictive of non–insulin-dependent gestational diabetes or early onset of gestational diabetes. There was a high prevalence of gestational diabetes in the Chinese population.

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New knowledge added by this study

- This is the first study to assess the association of first-trimester pregnancy–associated plasma protein-A multiple of median (PAPP-A MoM) with gestational diabetes mellitus (GDM) in a Chinese population. PAPP-A MoM was not predictive of development of non–insulin-dependent GDM in Chinese women.
- There was no correlation between PAPP-A MoM and glycosylated haemoglobin level in Chinese women with GDM. PAPP-A levels were not useful to predict and identify poor glycaemic control in women with GDM.
- There was a high prevalence of GDM (32.5%) in the Chinese population.

Implications for clinical practice or policy

- PAPP-A and β-human chorionic gonadotrophin do not seem to be predictive of non–insulin-dependent GDM. Other predictive model that comprises the maternal and clinical risk factors in Chinese women is warranted to identify women at risk of GDM.
- Further studies that employ the new diagnostic criteria for GDM are warranted to examine the potential of first-trimester biochemical markers to predict GDM as well as their influence on the prevalence of GDM in the Chinese population.

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of any degree that starts or is first recognised during pregnancy.[1] The prevalence of GDM in pregnant women varies widely in different populations and is highly dependent on the screening and diagnosis strategies that are used.[2] In the 1990s, the prevalence of GDM in Hong Kong was approximately 14.2%.[3] Studies in China and the United States show that the incidence of GDM has been increasing in recent years,[4,5] thus increasing the risk of complications for both mother and child during pregnancy, childbirth, and beyond.[6] Notably, it is reported that high first-trimester glucose levels are associated with an increased risk of a diagnosis of GDM later in pregnancy and adverse pregnancy outcome.[7] This suggests that women who will develop GDM can exhibit metabolic alterations early in pregnancy. Thus, it is of interest to determine whether pregnant women who develop GDM exhibit changes to first-trimester biochemical markers. If so, such markers can allow early detection and treatment of women at risk of GDM, and thus reduce the associated morbidity.[8,9]

In Hong Kong, all women undergo first-trimester screening for Down syndrome using a combination of maternal age, maternal free β-human chorionic gonadotrophin (β-HCG), pregnancy-associated plasma protein-A (PAPP-A), and fetal nuchal translucency (NT) thickness at 11–13+6 weeks of gestation. Studies have shown that low free β-HCG and PAPP-A levels in the first trimester are associated with pregnancy complications.[10,11] In particular, low PAPP-A levels are significantly associated with spontaneous fetal loss, low-birth-weight babies, intra-uterine growth restriction, pregnancy-induced hypertension, pre-eclampsia, preterm rupture of membranes, and placental abruption.[12-14] Several studies have shown that women with pre-existing diabetes mellitus (DM) have significantly lower PAPP-A levels than those without DM.[11,15-18] Besides, PAPP-A levels in non-pregnant individuals with type 2 DM correlate inversely with glycosylated haemoglobin (HbA1c) levels.[19] These observations suggest that PAPP-A levels may reflect the degree of glycaemic control. Studies of PAPP-A levels in patients with GDM have yielded conflicting results, however. In addition, such studies in Chinese women, who are well known to have a high prevalence of GDM, have not been performed.

The primary objective of this study was to investigate whether Chinese women with GDM exhibit changes in PAPP-A multiple of median (MoM) in the first trimester. The secondary objectives were to investigate whether PAPP-A level was an independent predictor of GDM, especially for early onset of GDM; whether PAPP-A MoM correlated with glycaemic control in women with GDM; and the prevalence of GDM in the Chinese population.

華籍婦女在早孕期的妊娠相關蛋白A水平與妊娠期糖尿病的相關性

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引言：研究顯示患有糖尿病的孕婦的妊娠相關蛋白A（PAPP-A）水平比無糖尿病的孕婦顯著低。本研究評估華籍婦女早孕期的PAPP-A水平的中位數測值的倍數值（MoM）是否與妊娠期糖尿病有關。

方法：這個前瞻性病例系列研究於香港一所分區醫院進行。所有於2014年4月至7月單胎妊娠並進行首次產前檢查（前14週妊娠）的華籍婦女均參與本研究。研究旨在比較妊娠期糖尿病組與非糖尿病孕婦的PAPP-A MoM值，並探討妊娠期糖尿病孕婦的PAPP-A水平與其糖化血紅蛋白水平的關係。

結果：520名婦女中，169人（32.5%）被診斷患有妊娠期糖尿病；當中43人（25.4%）屬早發妊娠期糖尿病，167人（98.8%）只須以飲食調節來控制病情。妊娠期糖尿病組與非糖尿病孕婦組在PAPP-A MoM值（0.97對0.99，P=0.40）或β人絨毛膜促性腺激素MoM值（1.05對1.02，P=0.29）並無顯著差異。與非糖尿病孕婦組比較，早發妊娠期糖尿病的婦女的PAPP-A MoM值較低，但成效未達顯著（中位數，四分範圍：0.86，0.57-1.23對0.99，0.67-1.44；P=0.11）。妊娠期糖尿病組中的PAPP-A水平和糖化血紅蛋白水平並無相關（r=0.027；P=0.74）。

結論：華籍婦女患有非胰島素依賴型妊娠期糖尿病與沒有患妊娠期糖尿病的PAPP-A MoM值並沒有顯著差異，其PAPP-A和糖化血紅蛋白水平也無相關性，可見PAPP-A MoM值不能預測非胰島素依賴型妊娠期糖尿病或早發妊娠期糖尿病。華籍婦女妊娠期糖尿病的發病率偏高。

Methods

This prospectively collected case series was conducted between April and July 2014 at the obstetric unit of Pamela Youde Nethersole Eastern Hospital, which is a public tertiary care hospital in Hong Kong. Ethical approval for the study was obtained from the local institutional human research ethics committee.

All consecutive Chinese women with a singleton pregnancy who attended the hospital for their first antenatal visit (before 14 weeks of gestation) during the recruitment period were invited to participate in this study. Written informed consent was obtained from all women who agreed to participate. Women with a multiple pregnancy, pre-existing DM, chronic disease (eg renal disease, hypertension, connective tissue disease), miscarriage, termination of pregnancy, a fetus with a chromosomal or congenital abnormality, or

preterm delivery before an oral glucose tolerance test (OGTT) could be performed were excluded.

Universal first-trimester Down syndrome screening was performed using fetal NT and maternal biochemistry. The ultrasound machine used was the Voluson E8 Expert (GE Healthcare, Fairfield [CT], US) or iU22 (Philips Medical System, Bothell [WA], US) equipped with a 3-5 MHz convex/broadband transducer. To determine crown rump length and NT thickness, the protocols outlined by the Fetal Medicine Foundation were followed.[20] The serum levels of free β-HCG and PAPP-A were measured by the DELFIA Xpress analytical platform (PerkinElmer Life Sciences, Turku, Finland). Multiple of median was adjusted for maternal weight and ethnicity. Down syndrome risk was calculated using the Alpha software (Logical Medical Systems, London, UK).
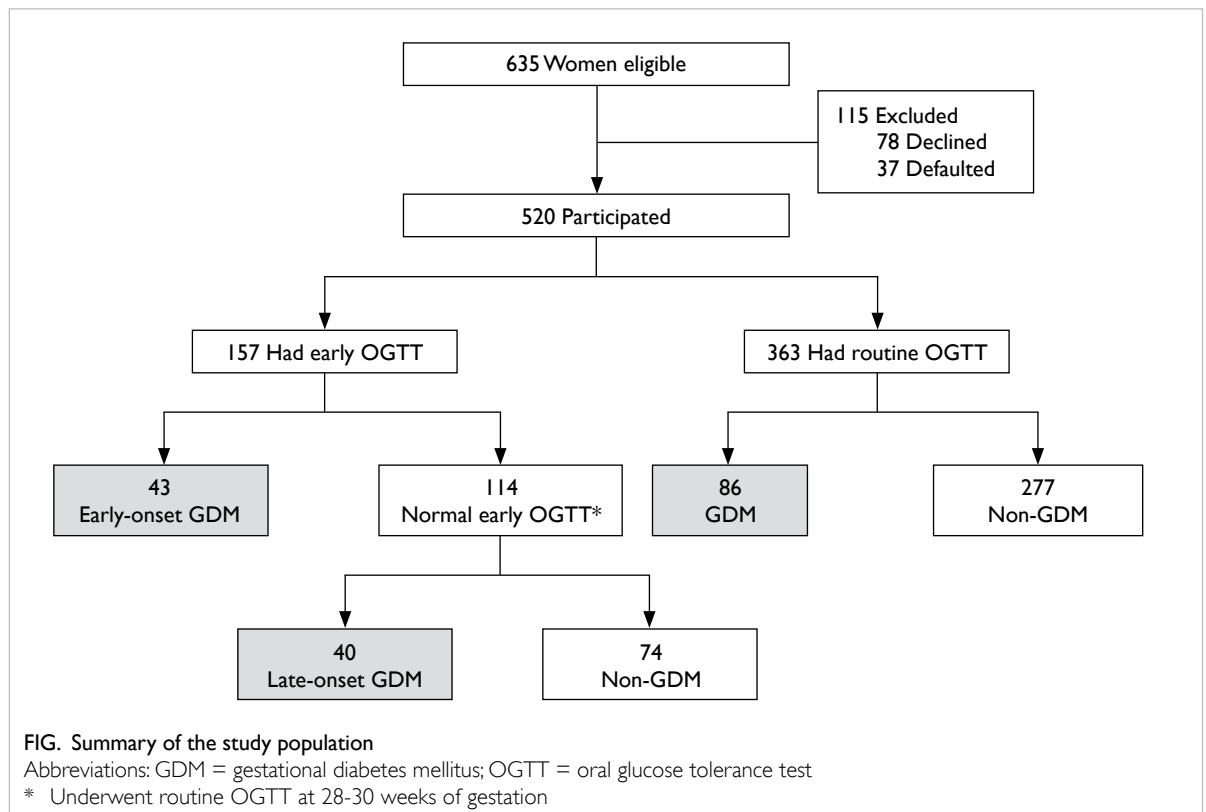
The demographic and clinical data were routinely collected by an obstetrician during the first antenatal visit and were entered into the hospital electronic system (antenatal record system). Maternal weight, height, and blood pressure were measured and body mass index (BMI) was calculated.

All women who had one or more risk factors for the development of GDM, such as advanced maternal age (≥35 years), previous GDM, family history of DM (first-degree relative with DM), a previous macrosomic baby (≥4.0 kg), an unexplained stillbirth, significant glycosuria, or obesity (BMI ≥25 kg/m²) underwent an early 75-g OGTT after the initial visit. The OGTT results were interpreted according to the World Health Organization (WHO) 1999 criteria.[21] Gestational DM was diagnosed if the fasting blood glucose level was ≥7.0 mmol/L or if the 2-hour OGTT blood glucose level was ≥7.8 mmol/L. All low-risk women and those with normal early OGTT results underwent universal 75-g OGTT screening at around 28 to 30 weeks. Women with a diagnosis of GDM underwent a further blood test 2 to 3 weeks after the initial diagnosis to determine HbA1c level. They were also given dietary and exercise advice and encouraged to perform daily capillary blood glucose monitoring before and 2 hours after a meal. If the pre- and post-meal glucose levels frequently exceeded 6.0 and 7.8 mmol/L, respectively, the women were prescribed insulin. All participating women received routine antenatal care until delivery according to our department protocol.

All statistical analyses were performed using PASW Statistics 18, Release Version 18.0.0 (SPSS Inc, 2009, Chicago [IL], US). Categorical data were analysed using the Chi squared test or Fisher's exact test, depending on the data distribution. For continuous variables with a normal distribution, the independent t test was used. For continuous data with a highly skewed distribution, a non-parametric test (ie Mann-Whitney U test) was used.

Sample size was calculated based on two assumptions. First, about 25% of the population

FIG. Summary of the study population
Abbreviations: GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test
* Underwent routine OGTT at 28-30 weeks of gestation

screened will have GDM, according to a previous local study[22] and our departmental annual audit. Second, there was a 10% difference in PAPP-A MoM between a GDM and non-GDM group, according to a previous published series.[23] Based on these assumptions, a total sample size of 380 cases with 95 cases in the GDM group and 285 cases in the non-GDM group were required for a type 1 error of 0.05, power of 80%, and standard deviation of 0.3 in both groups.

Results

The study sample is summarised in the Figure. In total, 520 women participated in the study of whom 157 (30.2%) underwent early OGTT. Indications for early OGTT are summarised in Table 1. Overall, GDM was diagnosed in 169 women. Among them, 43 (25.4%) had an early diagnosis of GDM. All GDM cases were diagnosed based on a 2-hour OGTT blood glucose level of ≥7.8 mmol/L; none had a fasting blood glucose level of ≥7.0 mmol/L (Table 2). The remaining 351 women did not develop GDM. The GDM prevalence was 32.5%. No woman underwent preterm delivery before OGTT. There was no difference in baseline characteristics between those excluded (eg defaulter and decliner) and those

included in the analysis. The majority (n=167; 98.8%) of women with GDM were managed with diet alone. Only two (1.2%) required insulin.

The maternal characteristics of the women with and without GDM are shown in Table 3. Compared with the non-GDM group, women in the GDM group were significantly older (34 vs 32 years), had a higher parity (1 vs 0) and a higher BMI (22.5 vs 21.3 kg/m^2). They were also more likely to have conceived with assisted reproductive technology and to have a family history of DM and a history of GDM. The two groups did not differ in terms of PAPP-A MoM (P=0.40) or free β-HCG MoM (P=0.29), however.

Compared with the non-GDM group, women with an early diagnosis of GDM had a non-significant reduction in PAPP-A MoM (median, interquartile range: 0.86, 0.57-1.23 vs 0.99, 0.67-1.44; P=0.11). There was also a non-significant reduction in PAPP-A MoM (median, interquartile range: 0.86, 0.57-1.23 vs 1.02, 0.72-1.61; P=0.07) in the women with early-onset GDM compared with those who had late-onset GDM (their early OGTT result was normal but subsequent routine OGTT result at 28 weeks was abnormal). Only two women with GDM required insulin treatment: their PAPP-A MoM was 0.54 and 0.78, which was low when compared with that of women with GDM who did not require insulin treatment or with the non-GDM group.

In this study, 308 (59.2%) women were nulliparous. Among them, GDM was diagnosed in 83 women. Compared with the non-GDM group, nulliparous women with GDM had no significant change in PAPP-A MoM (median, interquartile range: 0.92, 0.63-1.27 vs 1.0, 0.72-1.46; P=0.08).

Although univariate analysis showed that the women with and without GDM did not differ significantly in PAPP-A MoM, it is possible that an association between GDM and PAPP-A MoM was obscured by confounding variables. To identify potential confounding variables, Spearman's rho correlation coefficient analysis was performed (Table 4). It revealed that PAPP-A MoM did not correlate with maternal age, height, parity, or NT.

TABLE 1. Indications for early oral glucose tolerance test

Indication	No. (%) of participants
Advanced maternal age (≥35 years)	157 (100.0)
Obesity (BMI ≥25 kg/m^2)	95 (60.5)
Family history of DM*	123 (78.3)
Previous GDM	47 (29.9)
Previous macrosomic baby†	3 (1.9)
Previous unexplained stillbirth	0

Abbreviations: BMI = body mass index; DM = diabetes mellitus; GDM = gestational diabetes mellitus
*   First-degree relative(s) with diabetes mellitus
†   Birth weight ≥4.0 kg

TABLE 2. Prevalence of GDM and GDM diagnosed by each blood glucose measure with different diagnostic criteria

Criteria	Prevalence of GDM (%)	GDM diagnosed by each glucose measure		
		Fasting blood glucose ≥7.0 mmol/L*	2-Hour OGTT blood glucose ≥7.8 mmol/L†	Both fasting and 2-hour OGTT blood glucose‡
WHO 1999	32.5	0	169 (100%)	0
WHO 2013	18.5	11 (12%)	70 (76%)	11 (12%)

Abbreviations: GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test; WHO = World Health Organization
*   Only fasting blood glucose value is ≥ threshold
†   Only 2-hour blood glucose value is ≥ threshold
‡   Both fasting and 2-hour blood glucose values are ≥ threshold

TABLE 3. Demographic and clinical characteristics of women with and without GDM*

Characteristic	GDM (n=169)	Non-GDM (n=351)	P value†
Age (years)	34 (31-37)	32 (29-35)	<0.001
Advanced maternal age (≥35 years)	73 (43.2%)	84 (23.9%)	<0.001
Parity	1 (0-1)	0 (0-1)	0.002
Height (cm)‡	160 (156-163)	160 (156-164)	0.27
BMI (kg/m²)‡	22.5 (20.7-24.9)	21.3 (19.7-23.4)	<0.001
Obesity (BMI ≥25 kg/m²)	41 (24.3%)	54 (15.4%)	0.01
Systolic blood pressure (mm Hg)‡	107 (99-116)	106 (98-115)	0.16
Diastolic blood pressure (mm Hg)‡	63 (59-69)	62 (57-68)	0.14
Gestational age at USG (weeks)	12.3 (12.0-12.7)	12.4 (11.9-12.7)	0.84
Nuchal translucency (mm)	1.7 (1.5-2.0)	1.7 (1.4-2.0)	0.10
Free β-HCG (MoM)	1.05 (0.73-1.64)	1.02 (0.71-1.55)	0.29
PAPP-A (MoM)	0.97 (0.65-1.32)	0.99 (0.67-1.44)	0.40
Haemoglobin level (g/L)‡	128 (121-133)	127 (122-133)	0.56
Smoker	0	4 (1.1%)	0.40
ART	8 (4.7%)	2 (0.6%)	0.003
Family history of DM§	51 (30.2%)	72 (20.5%)	0.01
Previous GDM	40 (23.7%)	7 (2.0%)	<0.001
Previous macrosomic baby‖	1 (0.6%)	2 (0.6%)	1
Hepatitis B carrier	10 (5.9%)	21 (6.0%)	0.98
Alpha-thalassaemia trait	7 (4.1%)	12 (3.4%)	0.68

Abbreviations: ART = assisted reproductive technology; β-HCG = β-human chorionic gonadotrophin; BMI = body mass index; DM = diabetes mellitus; GDM = gestational diabetes mellitus; MoM = multiple of median; PAPP-A = pregnancy-associated plasma protein-A; USG = ultrasonography
* Continuous data are expressed as median (25th-75th percentile) and categorical data are expressed as No. (%)
† Continuous data were analysed by Mann-Whitney U test; categorical data were analysed by Pearson Chi squared test or Fisher's exact test
‡ Measurement obtained at first antenatal visit with gestational age of ≤14 weeks
§ First-degree relative with diabetes mellitus
‖ Birth weight ≥4.0 kg

TABLE 4. Correlations of pregnancy-associated plasma protein-A multiple of median with maternal demographic and clinical characteristics

Maternal characteristic	PAPP-A MoM (r)	P value*
Age	0.006	0.89
Height	0.035	0.42
Parity	-0.006	0.89
Free β-HCG (MoM)	0.2	<0.001
Nuchal translucency	-0.056	0.21

Abbreviations: β-HCG = β-human chorionic gonadotrophin; MoM = multiple of median; PAPP-A = pregnancy-associated plasma protein-A
* Continuous data were analysed by Spearman's rho correlation coefficient

There was a significant but weak correlation between PAPP-A MoM and free β-HCG MoM (r=0.2). Since univariate analysis showed that free β-HCG MoM was not associated with GDM (P=0.29), its confounding effect would be minimal. Thus, an association between GDM and PAPP-A MoM was not detected.

Our study showed that with maternal risk factor screening strategies, only 157 (30.2%) women would undergo OGTT (Fig). If we screened at-risk women by early OGTT alone, only 43 (25.4%) cases of GDM would be identified. On the other hand, if we subjected at-risk women to early OGTT followed by 28-week OGTT for those who had a normal early OGTT, 83 (49.1%) cases of GDM would be identified.

Although we lacked 1-hour data, we tried to determine whether PAPP-A was associated with GDM based on new diagnostic criteria from the American Diabetes Association (ADA), the International Association of Diabetes and Pregnancy Study Groups (IADPSG),[24] and WHO 2013.[25] A total of 23 women in whom GDM was diagnosed during early pregnancy based on WHO 1999 criteria (but normal by WHO 2013 criteria) did not undergo a second OGTT and were excluded from analysis. The

application of the fasting or 2-hour criteria led to 92 (18.5%) women being identified with GDM. The majority (76%) of women were diagnosed with GDM based on a 2-hour glucose level of ≥8.5 mmol/L (Table 2). Nevertheless, the GDM group again did not differ to the non-GDM group in terms of PAPP-A MoM (median, interquartile range: 0.94, 0.67-1.34 vs 0.99, 0.66-1.43; P=0.52) or free β-HCG MoM (1.02, 0.71-1.56 vs 1.03, 0.72-1.61; P=0.80).

To determine whether PAPP-A MoM and HbA1c levels in women with GDM correlated with each other, Spearman's rho correlation coefficient was used. A correlation was not found (r=0.027; P=0.74).

Discussion

The present study showed that Chinese women with GDM did not exhibit a significant change in PAPP-A MoM during the first trimester. Women with early-onset GDM had a non-significant decrease in PAPP-A MoM when compared with non-GDM women or women with late-onset GDM. Nevertheless, first-trimester PAPP-A MoM was not a useful predictor for development of GDM or early-onset GDM. This is consistent with the results of three other studies[18,26,27] but contradicts others.[8,9,11,23,28,29] These published series are summarised in Table 5.[8,9,11,18,23,26-29] There are several possible explanations

for the different results of these studies, including ours.

First, the studies differed in the selection criteria used to determine when OGTT should be performed, which in turn would target a different study population: some women were tested on the basis of GDM risk factors,[23] some when the women had an abnormal random blood glucose level[11,18] or 50-mg glucose challenge test,[9,28] others as a universal screening test as in our study.[8,27]

Second, the studies differed in terms of the OGTT method (75-g 2 hours, 100-g 3 hours, 100-g 2 hours) and diagnostic criteria. Tran et al[30] showed that GDM varied substantially in the same population by different diagnostic criteria: 5.9% ADA, 20.4% IADPSG, and 24.3% WHO 1999.

Third, the studies may differ in GDM severity, as reflected by the proportion of women with GDM who required insulin treatment. Women with GDM who require insulin may have a more severe type of GDM or undiagnosed pre-existing DM. Lovati et al[8] showed that women with GDM had a significantly lower PAPP-A MoM if they received insulin therapy than women with GDM who were managed by diet (0.56 vs 0.76 MoM; P<0.001). Beneventi et al[29] showed a similar result that PAPP-A MoM was significantly lower in GDM managed with insulin treatment than GDM without (0.87 vs 1.11 MoM; P=0.031). These studies showed that insulin-dependent GDM

TABLE 5. Summary of published studies on first-trimester biochemical marker concentrations in women who develop gestational diabetes mellitus[8,9,11,18,23,26-29]

Study	Study design	No. of women		GDM with insulin (%)	PAPP-A concentration (MoM)*		Free β-HCG concentration (MoM)*		OGTT test used for GDM diagnosis
		GDM	Control		GDM	Control	GDM	Control	
Ong et al, 2000[11]	Cohort	49	4297	NA	0.85 (0.69-1.0)†	1.05 (1.03-1.07)	0.78 (0.59-0.98)†	1.01 (0.98-1.04)	75 g (2 Hours)
Tul et al, 2003[26]	Cohort	27	1109	NA	0.98	1.01	0.86	0.99	100 g (2 Hours)
Beneventi et al, 2011[9]	Case control	228	228	NA	0.7 (0.5-1.2)†	1.2 (0.8-1.6)	0.9 (0.6-1.6)	1 (0.7-1.5)	100 g (3 Hours)
Savvidou et al, 2012[18]	Cohort	779	41007	41.7	0.94 (0.65-1.39)	1.0 (0.68-1.42)	0.95 (0.64-1.51)	1.0 (0.68-1.52)	75 g (2 Hours)
Husslein et al, 2012[27]	Case control	72	216	100	1.17 ± 0.71	1.13 ± 0.58	1.13 ± 0.73	1.15 ± 0.67	75 g (2 Hours)
Lovati et al, 2013[8]	Case control	307	366	24.4	0.9 ± 0.6†	1.3 ± 0.6	1.05 (0.7-1.6)	1.0 (0.7-1.6)	100 g (3 Hours, until March 2010) 75 g (2 Hours, from April 2010 onwards)
Kulaksizoglu et al, 2013[28]	Case control	60	60	40	0.77 ± 0.42†	0.97 ± 0.4	0.93 ± 0.53	0.97 ± 0.25	100 g (3 Hours)
Spencer and Cowans, 2013[23]	Cohort	870	6559	12	0.91†	1.0	0.93	1.0	75 g (2 Hours)
Beneventi et al, 2014[29]	Case control	112	112	23	1.06 ± 0.59†	1.22 ± 0.64	NA	NA	75 g (2 Hours)

Abbreviations: β-HCG = β-human chorionic gonadotrophin; GDM = gestational diabetes mellitus; MoM = multiple of median; NA = not available; OGTT = oral glucose tolerance test; PAPP-A = pregnancy-associated plasma protein-A

* Data are expressed as median (25th-75th percentile) or mean ± standard deviation

† P<0.05

was more strongly correlated with lower PAPP-A MoM. There were, however, only two (1.2%) women with GDM in our study who required insulin, a much lower frequency compared with other study populations (12%-100%).[8,9,11,18,23,26-29] Although both women had a lower PAPP-A MoM than women with non–insulin-treated GDM or non-GDM group, such a small proportion is insufficient to determine whether PAPP-A MoM differs significantly between women with insulin-treated GDM and non–insulin-treated women with GDM. The low frequency of insulin treatment in our study population may imply that the majority of affected Chinese women had mild GDM and may also explain why our study population did not exhibit changes in PAPP-A MoM during the first trimester.

Fourth, it is known that PAPP-A and free β-HCG are influenced by other maternal or pregnancy variables such as gestational age,[11] maternal weight,[9,28] and smoking.[26] Corrections for these variables were taken into account when calculating the MoM of PAPP-A and free β-HCG. While different laboratories may have corrected the MoM of PAPP-A and free β-HCG differently using maternal or pregnancy variables, this may have introduced bias in the assessment of the association between these biochemical markers and GDM.

The HAPO study led to considerable debate about the definition of GDM.[6,31] As a result, ADA, IADPSG,[24] and WHO 2013[25] have recently suggested that GDM is diagnosed on the basis of 75-g OGTT and fasting, 1-hour, or 2-hour glucose levels of ≥5.1, ≥10.0, and ≥8.5 mmol/L as the threshold, respectively. Since we had the fasting and 2-hour glucose data (1-hour glucose data were not available), we reclassified our patients with GDM accordingly. After reclassification, PAPP-A and free β-HCG MoM in women with GDM did not differ to that of women without GDM. Our reclassification had limitations, however. A total of 23 women who were diagnosed with GDM during early pregnancy using old WHO 1999 criteria (but normal by WHO 2013 criteria) did not undergo second OGTT so it is unknown whether their results of a second OGTT would be normal or diagnosed as GDM based on the new WHO criteria. Further studies that employ the new diagnostic criteria for GDM are warranted to explore the potential of using first-trimester biochemical markers to predict GDM.

During pregnancy, PAPP-A is produced by trophoblasts and is detectable in maternal blood 28 days after conception. An experimental model found that PAPP-A was a protease of insulin growth factor binding protein 4, regulating the activity of insulin-like growth factor (IGF).[32] This may be a plausible explanation for the association between PAPP-A and glycaemic control because the IGF axis is involved in glycaemic control. Human studies, however, have not provided clear evidence for a metabolic or biochemical mechanism that can explain a putative association between first-trimester PAPP-A levels and GDM. In one study, non-pregnant individuals with type 2 DM were found to have lower PAPP-A levels than non-diabetic controls, PAPP-A levels correlated inversely with HbA1c levels (r= –0.2; P=0.03).[19] Another study failed to detect this correlation in pregnant women with insulin-dependent DM.[17] Similarly, we identified no correlation between PAPP-A and HbA1c levels in women with GDM. These observations suggest that PAPP-A may not be useful for assessing or predicting glycaemic control in women with GDM due to the relatively short duration of women's exposure to GDM that is confined to the latter part of pregnancy. This is particularly so in Chinese as the majority of affected women, as we have demonstrated, have mild disease only. To our knowledge, our study is the first to address this issue in women with GDM.

Different tools to assess risk of GDM have been proposed and most have found that previous GDM is the best predictor of subsequent GDM.[33] In our population, the majority of women (59.2%) were nulliparous. We tried to investigate whether PAPP-A would be a possible predictor in this group of women. Our study showed that in nulliparous women with GDM, first-trimester PAPP-A MoM did not differ to that of women without GDM.

There is much debate about the screening strategies for GDM. Jensen et al[34] found that risk factor–based screening was as effective as universal screening: those not identified on risk factor screening were negligible compared with the high number successfully identified. However, this may not be the case with Chinese women whose ethnicity places them at risk of GDM.[35-37] Our study showed that with maternal clinical risk factor–based screening, less than one third of our population would undergo OGTT and about half of the GDM cases would be missed. Provided resources are available, universal screening should be considered in Chinese women.

Our study, which was based on universal screening, showed a high prevalence of GDM (32.5%). This prevalence was much higher than that of a study conducted by Ko et al[3] in the early 1990s (14.2%). It was also higher than the HAPO study cohort in 2000-2006[38] that reported a prevalence of GDM in Hong Kong of 14.4%. It is worth investigating this change in the trend of GDM prevalence in Hong Kong that may be due to increasing maternal obesity, adoption of a westernised diet and lifestyle, genetic shift, or other unknown factors. Some authors have proposed that with the new GDM diagnostic criteria, the prevalence of GDM may increase further.[23] This may not be the case in Chinese, however. The HAPO study[38] found that in Hong Kong, a higher

proportion (29%) of GDM was diagnosed based on a raised 2-hour glucose level than in other countries (6%-19%). Our study concurred with the HAPO study: all women diagnosed with GDM (WHO 1999) had a raised 2-hour glucose level only (Table 2). With the raised 2-hour glucose cut-off value in the new WHO diagnostic criteria (from ≥7.8 to ≥8.5 mmol/L), the prevalence of GDM in Chinese may not be raised. Our figure of reclassifying GDM using new diagnostic criteria without 1 hour did show a reduction in GDM prevalence. Further study using the full WHO 2013 diagnostic criteria to assess the prevalence of GDM in Chinese is warranted.

Departmental resources and limited manpower did not allow us to use the new WHO 2013 diagnostic criteria. Moreover, possible selection bias (eg defaulters and decliners) and possible confounding factors were not taken into account in the present study. Nevertheless all women in our study underwent routine OGTT to identify GDM, covering both low- and high-risk groups, whereas other studies were more likely to focus only on a high-risk group. Some previous studies[11,15,18] have also included women with pre-existing DM.

This was the first study to assess the association between first-trimester PAPP-A levels and GDM in a Chinese population. It showed that the vast majority of Chinese women with GDM did not require insulin nor exhibit significant change in PAPP-A MoM during the first trimester. First-trimester PAPP-A MoM was not a useful predictor for development of GDM. A correlation between PAPP-A and HbA1c levels was not observed. Our study showed a high prevalence of GDM at 32.5%, which is higher than that in previous studies.

Declaration

No conflicts of interest were declared by authors.

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