First Trimester Screening for Gestational Diabetes Mellitus with Maternal Factors and Biomarkers

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Mini-Summary

What does this study add to current knowledge?
• First trimester prediction model for gestational diabetes mellitus (GDM) with maternal characteristics and obstetric history achieves moderate predictability in Chinese population. Its screening performance is better than that of models with maternal characteristics alone and preeclampsia (PE)-specific biomarkers alone. Among the biomarkers of PE screening, mean arterial pressure (MAP) has been shown to be an independent predictor of GDM; however, its addition to the model with maternal characteristics and obstetric history does not improve the screening performance.

What are the main clinical implications?
• The inclusion of MAP in the model combining maternal characteristics and obstetric history does not improve the screening performance for GDM. Future studies are needed to explore the effect of blood pressure control from early pregnancy on preventing GDM.

Keywords
Gestational diabetes mellitus · Prediction · First trimester · Biomarker · Screening

Abstract

Introduction: This study aimed to identify risk factors among maternal characteristics, obstetric history, and first trimester preeclampsia-specific biomarkers that were associated with subsequent development of gestational diabetes mellitus (GDM) and evaluate the performance of the prediction models.

Methods: This study was a secondary analysis of a prospective cohort study. The performance of the prediction models was assessed by area under the receiver operating characteristic curve (AUROC).

Results: A total of 837 (8.9%) cases of GDM and 8,535 (91.1%) unaffected cases were included. The AUROC of the prediction model combining maternal characteristics and obstetric history (0.735) was better than that of the model utilizing maternal characteristics alone and preeclampsia (PE)-specific biomarkers alone (AUROC 0.566). Among the preeclampsia-specific biomarkers, the mean arterial pressure (MAP) contributed to the increasing
First Trimester Screening for Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is one of the most common complications during pregnancy that affects 2.8–30.1% of pregnancies in Asia [1, 2]. GDM is associated with short-term and long-term adverse outcomes in the mother and her offspring. GDM increases the risks of maternal and perinatal morbidities, such as the need of cesarean delivery, preeclampsia (PE), birth injury, fetal macrosomia, neonatal hypoglycemia, hyperinsulinemia, and need for neonatal unit admission [3–5]. Moreover, women with a previous history of GDM and the offspring of affected pregnancy are predisposed to type 2 diabetes mellitus, obesity, and cardiovascular and metabolic diseases in the future [6–10].

Evidence shows that the influence of GDM on fetal growth may have occurred prior to the diagnosis of the condition, which is usually performed between 24 and 28 weeks of gestation [6], and the benefits of interventions for GDM afterward are limited [7, 8]. In view of these reasons, earlier screening for women at high risk of subsequent diagnosis of GDM needs to be considered to enable earlier interventions, thus allowing improvement in maternal and perinatal outcomes.

Apart from the widely known risk factors, including increasing age and body mass index (BMI), previous GDM, Asian ethnicity, new biomarkers have been discovered to predict GDM in the first trimester in recent years, such as adiponectin [9, 10], sex hormone-binding globulin [9, 11], and C-reactive protein [12]. The role of the first trimester biomarkers for the screening of PE has also been explored. Several studies have found that biomarkers utilized for PE screening, such as mean arterial pressure (MAP) [13, 14], uterine artery pulsatility index (UtA-PI) [15], serum pregnancy-associated plasma protein-A (PAPP-A) [16–18], and placental growth factor (PIGF) [19, 20], are significantly different between women with GDM and those without, suggesting that these biomarkers might be useful for the prediction of GDM. However, there are also other studies reporting contradictory results [15, 16, 21–23]. Whether the predictive performance for GDM based on maternal factors can be improved with the addition of PE-specific biomarkers is of interest.

We hypothesized that the prediction of GDM using maternal factors can be improved with the addition of PE-specific biomarkers. This study aimed to identify risk factors among maternal characteristics, obstetric history, and first trimester PE-specific biomarkers that were associated with subsequent development of GDM and evaluate the performance of the prediction models based on various combinations of maternal factors and biomarkers in the early detection of GDM in Chinese population.

Materials and Methods

This was a secondary analysis of data from a prospective cohort study for first trimester screening for PE in singleton pregnancies at 11–13 +6 weeks of gestation in women attending for routine Down syndrome screening at Prince of Wales Hospital, Hong Kong SAR, between December 09, 2016, and December 31, 2019. Approval for the study was obtained from the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2016.152) in Hong Kong. The study is registered with ClinicalTrials.gov (Identifier: NCT03554681). All eligible women were given written information about the study, and those who agreed to participate provided written informed consent. Gestational age was determined from the measurement of the fetal crown-rump length [24].

Inclusion criteria for the study were age ≥18 years old; singleton pregnancy; live fetus at the 11–13 +6 weeks’ scan; and subsequently delivering a phenotypically normal live birth at ≥24 weeks of gestation. Exclusion criteria were women who were unconscious or severely ill, those with learning difficulties or serious mental illness, major fetal abnormality identified at the 11–13 +6 weeks’ scan, and those with preexisting diabetes mellitus.

The first trimester screening for PE was based on the Fetal Medicine Foundation (FMF) triple test, which combined maternal characteristics, obstetric and medical history, MAP, UtA-PI, and serum PIGF [25]. In our setting, serum PAPP-A was measured as part of the first trimester screening for Down syndrome, but it could also be utilized for PE screening. The MAP was measured by validated automated blood pressure devices (BP3AQ1 Microlife, Taipei, Taiwan) according to a standardized protocol [26, 27]. Transabdominal pulsed wave Doppler ultrasound was used to measure the mean UtA-PI of the left and right uterine arteries. All operators undertaking the Doppler studies had received the appropriate Certificate of Competence from the FMF [28]. Serum PAPP-A and PIGF concentrations were measured by B-R-A-H-M-S KRYPTOR analyzers (Thermo Fisher Scientific, Hennigsdorf, Germany).

Participants were requested to complete a questionnaire and provide the following information: date of birth, age, racial origin (East Asian, South Asian, Caucasian, Afro-Caribbean, and mixed), cigarette smoking during pregnancy (yes or no), method of concep-
tion (spontaneous conception, ovulation induction, or in vitro fertilization [IVF]), obstetric history including parity, for parous women details of previous pregnancies including inter-pregnancy interval between the last and current pregnancy (defined as the period between previous delivery and conception of the current pregnancy), gestation age and birth weight of last pregnancy, prior history of PE (yes or no), prior history of GDM (yes or no), family history of PE in the mother of the participant (yes or no), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome (yes or no), and aspirin intake (yes or no). Maternal weight and height were measured, and BMI was calculated in kg/m². The questionnaire was subsequently reviewed by a dedicated researcher and recorded in a secure electronic database.

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. Our hospital provides targeted screening for GDM. High-risk pregnant women with any risk factor identified at the booking visit were offered 75 g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. Risk factors included advanced maternal age ≥35 years, BMI ≥25 kg/m² before pregnancy or at booking in the first trimester, family history of diabetes mellitus in first-degree relatives, polycystic ovarian syndrome, autoimmune disease, chronic hypertension, long-term use of diabetogenic medication such as systemic corticosteroids and tacrolimus, previous macromesonic neonate (birth weight ≥4 kg), and previous GDM. Women who presented with the following clinical features in the index pregnancy were also offered OGTT: large-for-date fetus (abdominal circumference or estimated fetal weight ≥90th percentile), polyhydramnios or glycosuria (≥2+ on one occasion or ≥1+ on two or more occasions detected by reagent strip testing) [29]. The primary outcome was diagnosis of GDM, which was defined according to the World Health Organization 2013 criteria [30]. GDM was diagnosed at any time in pregnancy if one or more of the following 75 g OGTT criteria were met and without diabetes mellitus before pregnancy: fasting plasma glucose 5.1–6.9 mmol/L, 1-h plasma glucose ≥10.0 mmol/L, or 2-h plasma glucose 8.5–11.0 mmol/L [30]. Women with diabetes in pregnancy were excluded in this study, which was diagnosed if one or more of the following criteria were met: fasting plasma glucose ≥7.0 mmol/L, 2-h plasma glucose ≥11.1 mmol/L, or random plasma glucose ≥11.1 mmol/L in the presence of diabetes symptoms [30].

Statistical Analysis

Normality of data was assessed using Kolmogorov-Smirnov test. Descriptive data were presented in median and interquartile range for continuous variables and in counts and percentages for categorical variables. Comparison between the outcome groups was by Mann-Whitney U test for continuous variables and χ² test and continuity correction test for categorical variables.

Measured values of MAP, UtA-PI, PAPP-A, and PI GF were converted into multiples of the median (MoM) adjusting for characteristics that were found to provide a substantive contribution to the log10 transformed value that included maternal characteristics in the a priori risk model [31, 32]. PI GF MoM was recentered by dividing by 0.84 to recenter the median in pregnancies without GDM at 1 MoM [33]. All MoMs were then log10 transformed prior to further analysis. The observed birth weight of the last pregnancy was expressed as a Z-score (difference between observed and expected mean birth weight, divided by the fitted standard deviation) corrected for gestational age at delivery [34].

Univariate logistic regression analysis was used to investigate the association between maternal characteristics, obstetric history, log10 transformed biomarkers, and the risk of subsequent development of GDM. Significant factors were identified if p < 0.2 and included in multivariate regression analysis for the prediction of GDM. Four types of multivariate regression models were established, which consisted of maternal characteristics (model 1), biomarkers of PE screening (model 2), maternal characteristics and obstetric history (model 3), maternal characteristics, obstetric history, and biomarkers of PE screening (model 4). The performance of the four prediction models for the screening of GDM was assessed by receiver operating characteristic curve. The area under the receiver operating characteristic curve (AUROC) and detection rates at fixed false-positive rates (FPRs) of 5%, 10%, 15%, and 20% were presented. The differences in AUROC between the four prediction models were compared using the DeLong test [35]. Statistical software package SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 19.1 (MedCalc Software, Mariakerke, Belgium) were used for data analyses.

Results

The total study population consisted of 11,029 women with singleton pregnancy that underwent first trimester screening for PE during the study period (Fig. 1). 1,657 (15.0%) cases were excluded due to lost to follow-up (n = 1,358), pregnancy loss (n = 112), termination of pregnancy (n = 97), and preexisting diabetes mellitus (n = 90). None were diagnosed with diabetes in pregnancy. The remaining 9,372 cases consisted of 837 cases (8.9%) of GDM and 8,535 (91.1%) cases of unaffected pregnancies. Characteristics and delivery outcomes of each outcome group are presented in Table 1.

In univariate analysis, maternal characteristics associated with GDM were maternal age, height, weight, BMI, conception by IVF, and chronic hypertension; obstetric history associated with GDM was multiparity, inter-pregnancy interval, gestational age, and birth weight Z-score of last pregnancy and previous GDM; and first trimester biomarkers associated with GDM were log10 MAP MoM and log10 PAPP-A MoM (shown in Table 2). In multivariate regression analysis, significant independent contributions were provided by maternal age, height, BMI, conception by IVF, and chronic hypertension in model 1; log10 MAP MoM and log10 PAPP-A MoM in model 2; maternal age, height, BMI, inter-pregnancy interval, birth weight Z-score of last pregnancy, and previous GDM in model 3; and maternal age, height, BMI, birth weight Z-score of last pregnancy, previous GDM, and log10 MAP MoM in model 4 (shown in Table 2, online suppl. Table 1; see www.karger.com/doi/10.1159/000525384 for all online suppl. material).
Table 1. Characteristics and delivery outcomes in women with and without GDM

| Characteristics                              | GDM (n = 837)   | Unaffected pregnancy (n = 8,535) | p value |
|----------------------------------------------|-----------------|----------------------------------|---------|
| Maternal age, years                         | 35.23 (31.91–37.51) | 32.48 (29.56–35.43)             | <0.001  |
| Height, cm                                   | 157 (154–161)   | 158 (155–162)                   | <0.001  |
| Weight, kg                                   | 58.5 (52.2–64.6) | 53.9 (49.2–59.9)                | <0.001  |
| BMI, kg/m²                                   | 23.54 (21.27–26.04) | 21.48 (19.78–23.68)            | <0.001  |
| Conception method                            |                 |                                  |         |
| Spontaneous or OI                           | 775 (92.6)      | 8,222 (96.3)                    | <0.001  |
| IVF                                          | 62 (7.4)        | 313 (3.7)                       | <0.001  |
| Smoking                                      | 63 (7.5)        | 604 (7.1)                       | 0.629   |
| Chronic hypertension                         | 9 (1.1)         | 17 (0.2)                        | <0.001  |
| SLE/APS                                      | 3 (0.4)         | 14 (0.2)                        | 0.403   |
| Multiparous                                  | 483 (57.7)      | 4,018 (47.1)                    | <0.001  |
| Inter-pregnancy interval, years              | 3.33 (1.92–6.0) | 3.08 (1.83–4.92)                | <0.001  |
| Gestational age of last pregnancy, weeks     | 39.43 (38.14–40.0) | 39.57 (38.43–40.0)             | 0.543   |
| Birth weight Z-score of last pregnancy       | −0.40 (−0.97 to 0.23) | −0.63 (−1.16 to 0.01)         | <0.001  |
| Previous GDM                                 | 69 (14.3)       | 85 (2.1)                        | <0.001  |
| Previous PE                                  | 3 (0.6)         | 26 (0.6)                        | 1.000   |
| Standardized biomarker levels                |                 |                                  |         |
| Log₁₀ MAP MoM                                | −0.0077 (−0.0331 to 0.0219) | −0.0155 (−0.0405 to 0.0117)    | <0.001  |
| Log₁₀ PAPP-A MoM                             | −0.0036 (−0.1470 to 0.1398) | 0.0190 (−0.1288 to 0.1557)    | 0.012   |
| Log₁₀ UtA-PI MoM                             | 0.0251 (−0.0512 to 0.1068) | 0.0336 (−0.0454 to 0.1042)    | 0.451   |
| Log₁₀ PlGF MoM                               | −0.0113 (−0.1462 to 0.1041) | −0.0013 (−0.1263 to 0.1159)   | 0.157   |
| Delivery outcomes                            |                 |                                  |         |
| Gestational age, weeks                       | 38.71 (38.14–39.71) | 39.29 (38.43–40.14)           | <0.001  |
| Fetal birth weight, kg                       | 3.15 (2.86–3.41) | 3.12 (2.87–3.38)                | 0.280   |

Numerical variables are presented in median (interquartile range), and categorical variables are presented in n (%). BMI, body mass index; GDM, gestational diabetes mellitus; MAP, mean arterial pressure; IVF, in vitro fertilization; MoM, multiples of the median; OI, ovulation induction; PAPP-A, pregnancy-associated plasma protein-A; PE, preeclampsia; PlGF, placental growth factor; SLE/APS, systemic lupus erythematosus/antiphospholipid syndrome; UtA-PI, uterine artery pulsatility index.

Fig. 1. Flowchart for the included study population.
### Table 2. Maternal characteristics, obstetric history, and biomarkers of PE screening in current pregnancy associated with GDM

|                          | Univariate analysis | Multivariate regression analysis |
|--------------------------|---------------------|----------------------------------|
|                          | OR (95% CI)         | p value                          | OR (95% CI)         | p value                          | OR (95% CI)         | p value                          | OR (95% CI)         | p value                          |
| Maternal age             | 1.140 (1.121–1.161) | <0.001                           | 1.123 (1.103–1.143) | <0.001                           | 1.115 (1.086–1.146) | <0.001                           | 1.121 (1.092–1.150) | <0.001                           |
| Height                   | 0.971 (0.958–0.983) | <0.001                           | 0.979 (0.967–0.992) | 0.02                             | 0.968 (0.950–0.986) | 0.001                           | 0.968 (0.949–0.986) | 0.001                           |
| Weight                   | 1.044 (1.037–1.051) | <0.001                           | 1.150 (1.129–1.172) | <0.001                           | 1.135 (1.113–1.157) | <0.001                           | 1.103 (1.074–1.134) | <0.001                           |
| BMI                      | 2.101 (1.585–2.787) | <0.001                           | 2.101 (1.585–2.787) | <0.001                           | 1.469 (1.093–1.973) | 0.011                           | 1.096 (1.066–1.127) | <0.001                           |
| Chronic hypertension     | 5.446 (2.420–12.256) | <0.001                           | 5.446 (2.420–12.256) | <0.001                           | 3.217 (1.375–7.528) | 0.007                           |                                    |                                |
| Multiparous              | 1.534 (1.329–1.771) | <0.001                           | 1.534 (1.329–1.771) | <0.001                           |                                    |                                |                                    |                                |
| Inter-pregnancy interval | 1.082 (1.061–1.103) | <0.001                           | 1.082 (1.061–1.103) | <0.001                           |                                    |                                |                                    |                                |
| Gestational age of last pregnancy | 0.956 (0.904–1.010) | 0.109                           |                                    |                                |                                    |                                |                                    |                                |
| Birth weight Z-score of last pregnancy | 1.277 (1.157–1.410) | <0.001                           |                                    |                                |                                    |                                |                                    |                                |
| Previous GDM             | 8.932 (5.446–12.375) | <0.001                           |                                    |                                |                                    |                                |                                    |                                |
| Log10 MAP MoM            | 288.211             | <0.001                           | 288.211             | <0.001                           |                                    |                                |                                    |                                |
| (47.967–1.731708)       |                     |                                  | (45.996–1.644921) |                                  |                                    |                                | (6.793–1.021147) |                                  |
| Log10 PAPP-A MoM         | 0.660 (0.473–0.921) | 0.015                            | 0.660 (0.473–0.921) | 0.015                            |                                    |                                |                                    |                                |

Model 1 consisted of maternal characteristics; model 2 consisted of biomarkers of PE screening; model 3 consisted of maternal characteristics and obstetric history; model 4 consisted of maternal characteristics, obstetric history, and biomarkers of PE screening. BMI, body mass index; GDM, gestational diabetes mellitus; MAP, mean arterial pressure; IVF, in vitro fertilization; MoM, multiples of the median; PAPP-A, pregnancy-associated plasma protein-A.

### Table 3. Comparisons of AUROC for the screening of GDM by maternal characteristics, obstetric history, and biomarkers of PE screening in current pregnancy

| Screening test for GDM | AUROC | SE   | 95% CI  | Comparison of the AUROC          | model 1                  | model 2                  | model 3                  | model 4                  |
|------------------------|-------|------|---------|----------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Model 1                | 0.708 | 0.0092 | 0.699–0.717 | –                               | 0.128 (0.0924–0.163)* | 0.0368 (0.0216–0.519)* | 0.0399 (0.0244–0.0557)* | –                       |
| Model 2                | 0.566 | 0.0106 | 0.555–0.576 | 0.128 (0.0924–0.163)*           | –                       | 0.165 (0.129–0.200)* | 0.168 (0.136–0.199)* | –                       |
| Model 3                | 0.735 | 0.0121 | 0.722–0.748 | 0.0368 (0.0216–0.519)*           | 0.165 (0.129–0.200)* | –                       | 0.00312 (–0.00361 to 0.00985) | –                       |
| Model 4                | 0.738 | 0.0123 | 0.725–0.751 | 0.0399 (0.0244–0.0557)*           | 0.168 (0.136–0.199)* | 0.00312 (–0.00361 to 0.00985) | –                       | –                       |

Model 1 consisted of maternal characteristics; model 2 consisted of biomarkers of PE screening; model 3 consisted of maternal characteristics and obstetric history; model 4 consisted of maternal characteristics, obstetric history, and biomarkers of PE screening. AUROC, area under the receiver operating characteristic curve; CI, confidence interval; GDM, gestational diabetes mellitus; SE, standard errors. * p < 0.05.
The AUROCs of the four different models in predicting GDM by first trimester screening are demonstrated in Table 3. The AUROC of the model utilizing factors of maternal characteristics alone (model 1) and first trimester biomarkers alone (model 2) was 0.708 (95% confidence interval [CI] 0.699–0.717) and 0.566 (95% CI 0.555–0.576), respectively. The AUROC was significantly improved when utilizing factors of maternal characteristics and obstetric history (model 3) (AUROC 0.735 [95% CI: 0.722–0.748]; the differences between the AUROCs of model 3 compared to model 1 and model 2 were 0.0368 [p < 0.001] and 0.165 [p < 0.001], respectively. The predictive performance for GDM did not improve when MAP was added to the model combining factors of maternal characteristics and obstetric history (namely model 4) (AUROC 0.738 [95% CI: 0.725–0.751]; the difference between the AUROC of model 4 compared to model 3 was 0.00312 [p = 0.363] (shown in Table 3). The detection rates of each model at 5%, 10%, 15%, and 20% fixed FPR are presented in Table 4.

Discussion

The study has demonstrated that, first, in the first trimester combined model for the prediction of GDM including maternal characteristics, obstetric history, and biomarkers of PE screening, significant independent predictors are maternal age, height, BMI, birth weight Z-score of last pregnancy, previous GDM, and log10 MAP MoM; second, the predictive performance of the multivariate model for GDM utilizing maternal characteristics and obstetric history is better than that of the model with maternal characteristics alone and the model with biomarkers of PE screening alone, while the addition of MAP does not improve the model with maternal characteristics and obstetric history. The association of increased maternal age, height, BMI, and previous GDM with the development of GDM is consistent with existing literature. Syngelaki et al. [36] demonstrated that maternal age, weight, height, racial origin, family history of diabetes mellitus, use of ovulation drugs, previous birth weight, and previous history of GDM were significant first trimester predictors of subsequent development of GDM [36]. When utilizing this model for the screening of GDM in singleton pregnancies, at 10% and 20% FPR, the detection rates were 42.8% and 58.0%, respectively [37]. Our results have shown comparable predictive performance utilizing maternal characteristics and obstetric history (model 3), with detection rates of 35.6% (95% CI: 32.3–41.7) and 53.0% (95% CI: 48.2–57.7) at 10% and 20% FPR, respectively.

The AUROC for the prediction of GDM has significantly improved when factors from the obstetric history are added to maternal characteristics. Although the significant difference between the AUROC of these two models is only 0.03, all the factors of obstetric history are readily available in clinical practice; therefore, it is reasonable to include factors from the obstetric history in order to improve the screening performance for GDM.

Previous large-for-gestational-age baby is a recognized risk factor for subsequent GDM [9, 30, 36], while the association between the standardized birth weight corrected for gestational age in a previous pregnancy and the risk of GDM has not been clearly described in the literature. Only two previous studies have reported on the relationship between birth weight Z-score of last pregnancy and risk of GDM, and both studies have demonstrated that the birth weight Z-score of last pregnancy is

Table 4. Detection rate and FPR for the screening of GDM by prediction models based on maternal characteristics, obstetric history, and biomarkers of PE screening in current pregnancy

| Detection rate | Fixed FPR |
|----------------|-----------|
|                | 5%        | 10%       | 15%       | 20%       |
| Model 1        | 16.97 (14.22–19.83) | 29.63 (25.81–33.81) | 39.19 (35.9–42.6) | 48.03 (44.20–51.61) |
| Model 2        | 8.46 (6.47–10.57) | 15.60 (12.94–18.41) | 23.38 (20.5–26.5) | 28.11 (25.00–31.59) |
| Model 3        | 24.32 (19.71–28.93) | 35.64 (32.29–41.72) | 44.23 (39.7–48.8) | 53.04 (48.22–57.65) |
| Model 4        | 25.55 (22.05–30.35) | 36.68 (32.10–41.05) | 45.20 (40.6–49.9) | 51.53 (46.29–56.33) |

Model 1 consisted of maternal characteristics; model 2 consisted of biomarkers of PE screening; model 3 consisted of maternal characteristics and obstetric history; model 4 consisted of maternal characteristics, obstetric history, and biomarkers of PE screening.
an independent predictor for the screening of GDM after adjusting for other maternal characteristics [36, 37]. The present study has demonstrated that for every unit increase of birth weight Z-score of last pregnancy from the mean (Z-score 0) there is a 23% increase in the risk of GDM (OR 1.23, 95% CI: 1.10–1.37); in other words, the risk of GDM is not only limited to previous history of macrosomia or large for gestational age but also increases with birth weight Z-score of last pregnancy.

Among the biomarkers of PE screening, the findings that MAP is increased and PAPP-A is decreased in women who will subsequently develop GDM are consistent with the majority of previous studies. A retrospective study by Li et al. [14] has measured MAP level among 6,104 pregnant women before 20 weeks of gestation and concluded that after adjustment for maternal age, BMI, ethnicity, marital status, and family history of diabetes mellitus and chronic hypertension in a logistic regression analysis, every 1 mm Hg increase in MAP level confers a 1.035-fold increase in risk of GDM. Our multivariate regression model that combines maternal characteristics, obstetric history, and biomarkers of PE screening (model 4) has demonstrated that each unit increase of MoM value of MAP increases the risk of subsequent GDM by 6.459-fold (95% CI: 2.208–18.898). The evidence for whether serum PAPP-A can be utilized to predict GDM remains inconsistent, and in our study, serum PAPP-A is excluded from the model after adjusting for maternal characteristics and obstetric history.

Regarding the reason why elevated MAP is related to an increased risk of GDM, Osman et al. [13] have demonstrated that alterations of central hemodynamics, such as increased cardiac output (CO), stroke volume (SV), MAP, and arterial stiffness, have been observed in women identified as high risk for GDM as defined by the National Institute for Health and Clinical Excellence guidelines, compared to low-risk healthy pregnant women at 26–28 weeks of gestation. The increase in CO seen in women at high risk for GDM may be related to the higher maternal weight and BMI, as obese individuals have higher hemodynamics workload partially due to the augmented metabolic demand [38]. The increased blood volume affects the SV and therefore increases the CO [39], which then regulates the MAP [40]. Our results have revealed that the elevation of MAP, which is likely as a result of increase in SV and CO, may present as early as in the first trimester of pregnancy. The higher arterial stiffness is associated with cardiovascular complications, such as systolic hypertension and coronary artery disease. Although the association between higher MAP and increasing risk of GDM is still under debate, hypertension (characterized by vascular dysfunction and injury) is known to be an important risk factor of diabetes-associated vascular diseases, and related vascular mechanisms include upregulation of the renin-angiotensin-aldosterone system, oxidative stress, inflammation, and activation of the immune system [41]. Furthermore, arterial stiffness has been shown to be associated with insulin resistance, which is the underlying pathophysiology of GDM [42]. Alterations of arterial stiffness before the diagnosis of GDM may reflect the preclinical influence of hyperglycemia and hypertension on the vascular walls during pregnancy, which is possibly connected to future development of diabetes.

We were reporting results based on a large prospective cohort study in evaluating the potential role of first trimester biomarkers of PE screening for the prediction of GDM in Chinese population. Another strength was that we collected complete data on previous history of GDM and birth weight Z-score of last pregnancy. Furthermore, all measured biomarker values of PE screening were acquired in a standardized systematic approach with all biomarkers adjusted for covariates affecting their individual levels. The main limitation of our study was that OGTT testing was based on a targeted screening approach; therefore, we might have underestimated the incidence of GDM. In spite of this, the overall incidence of GDM in our study was in keeping with the existing literature. Another limitation was that the wide CI of the OR of MAP in predicting GDM suggested that model 4 was not sufficiently powered. This was in line with the findings that the predictive performance for GDM utilizing factors of maternal characteristics and obstetric history did not improve with the addition of MAP. A prospective evaluation of the efficacy of MAP in predicting GDM in an independent cohort is needed. Furthermore, the detection rates of models 1, 3, and 4 for the prediction of GDM were about 50%, for a 20% FPR, which would be considered suboptimal for the early prediction of GDM. In view of this, more effort is needed to identify other biomarkers to improve the screening performance for GDM.

In conclusion, our study has demonstrated that the first trimester prediction model for GDM with maternal characteristics and obstetric history achieves moderate predictability with AUROC at 0.735. Among the biomarkers of first trimester PE screening, the MAP contributes to the increasing risk of GDM. However, the inclusion of MAP in the model combining maternal characteristics and obstetric history does not improve the screening
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performance for GDM. Future studies are needed to explore the effect of blood pressure control from early pregnancy on preventing GDM. More research is required to discover other potential first trimester biomarkers for the prediction of GDM.

Statement of Ethics

Approval for the study was obtained from the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2016.152) in Hong Kong. All eligible women were given written information about the study, and those who agreed to participate provided written informed consent. The present research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflicts of Interest Statement

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Author Contributions

Lixia Shen performed the statistical analysis and wrote the manuscript. Daljit S. Sahota collected the study data, performed the statistical analysis, and reviewed the manuscript. Piya Chaimsaithong contributed to the planning of the study, collected study data, and reviewed the manuscript. Wing Ting Tse, Man Yan Chung, and Jeffery Ka Him Ip collected the study data. Tak Yeung Leung reviewed the manuscript. Liona Chiu Yee Poon designed the study, collected the study data, and revised the manuscript critically.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.
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