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Importance of early elevated maternal HbA1c levels in identifying adverse fetal and neonatal events

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ABSTRACT

Aims: The aims of this study were to explore factors that associated with gestational diabetes mellitus (GDM), and to determine the relationship between early maternal HbA1c levels and adverse fetal or neonatal events, and to determine an optimal maternal glucose testing method in order to decrease the potential health risk for their offspring.

Methods: From December 2015 to May 2016, a total of 6744 pregnant women were enrolled from Shanghai First Maternal and Infant Hospital affiliated to Tongji University prospectively in the nested case-control study. Each GDM case was matched with a healthy pregnant woman and followed up. Outcome analyses were conducted between GDM case and control groups, as well as elevated and normal maternal HbA1c levels, respectively.

Results: A total of 1836 women were included in the adverse fetal and neonatal events examination. For pregnant women with early HbA1c ≥ 5.2%, the adjusted risk ratios (RR) of respiratory distress syndrome (RDS), pneumonia and jaundice were 4.37 (95%CI 1.54–12.35), 2.03 (95%CI 1.24–3.33) and 1.49 (95%CI 1.01–2.20), respectively. After treatments, the frequency for the majority of events in GDM group was similar to that of healthy pregnant women. Moreover, the area under the curve (AUC) of early maternal HbA1c in predicting potential RDS is 0.734. HbA1c ≤ 4.9% excluded for RDS.

Conclusions: Compared with women with normal HbA1c, those with an early elevated HbA1c level were more likely to develop adverse events, including RDS, pneumonia and jaundice. Early HbA1c testing can be used as an auxiliary method identifying potential RDS.

1. Introduction

The risk of adverse maternal and neonatal events has recently been demonstrated to be linearly associated with rising maternal glucose levels [1]. Although treatment of impaired glucose tolerance and gestational diabetes mellitus (GDM) in pregnancy can reduce perinatal morbidity, frequency of preeclampsia, macrosomia, congenital and other complications, as well as improve perinatal outcomes [2–8], they are still associated with major potential risks, which can severely jeopardize the quality of life for their offspring [9,10]. Respiratory distress syndrome (RDS) remains one of the most significant problems faced by preterm neonates. In order to maximize survival whilst minimizing potential adverse effects, a recent study has provided a series of intervention guidelines [11]; however, the frequency of severe bronchopulmonary dysplasia (BPD) has actually increased [12]. In addition, jaundice is a common symptom in neonates, and although the majority of cases are benign, neonates with severe hyperbilirubinemia can develop acute bilirubin encephalopathy or kernicterus due to the potential toxicity of bilirubin [13]. Moreover, in 2013 alone, neonatal pneumonia accounted for 0.935 million or 14.9% of all deaths in children under 5 years of age, worldwide [14].

In order to avoid adverse events, pregnant women with GDM who were diagnosed according to the 75-g oral glucose-tolerance test (OGTT) threshold from current guidelines, often receive professional

Abbreviations: AUC, area under the curve; GDM, gestational diabetes mellitus; RDS, respiratory distress syndrome; RR, relative ratio

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advice during the prenatal period. However, due to the abundance of risk factors that are often ambiguous in nature, the threat of adverse events in their offspring remains high. Compared with OGTT, HbA1c test is an easier, more acceptable, and reproducible assessment that causes minimal discomfort to patients [15]. It is also a separate indicator of blood glucose, which provides an integrated summary of circadian blood glucose level during the preceding 6–8 weeks, and therefore, HbA1c can better reflect the mean blood glucose level of early pregnancy [16]. It has been confirmed that increasing maternal HbA1c levels within the normal range is associated with adverse outcomes in women without pre-existing diabetes [17]. However, the potential impact of early maternal HbA1c levels on the prediction of some severe events is yet unclear.

The aims of this study were to explore factors that are associated with GDM, and to determine the relationship between early maternal HbA1c levels and adverse fetal or neonatal events. Furthermore, our study aimed to determine an optimal glucose testing method in order to decrease the potential health risk for neonates.

2. Materials and methods

2.1. Study design and recruitment

Initially, we conducted a prospective nested case-control study to investigate the risk factors associated with GDM. Subsequently, subjects were followed up to determine the relationship between early maternal HbA1c levels and adverse fetal or neonatal events, prospectively. From December 2015 to May 2016, a total of 6744 pregnant women were enrolled from Shanghai First Maternity and Infant Hospital affiliated to Tongji University School of Medicine as a consecutive case series at the time of their first antenatal visit. The study was approved and waived of informed consent by the institutional review board of Tongji University.

2.2. GDM cases and selection of controls

The basic work flow of participant recruitment and case–control selection was shown in Fig. 1. As it is routine in China, pregnant women underwent an assessment of HbA1c during early pregnancy (12–20 weeks of gestation) and a standard fasted 75-g oral glucose-tolerance test (OGTT) was administered at 24–28 weeks of gestation, respectively. Women who could not tolerate the tests were excluded from the study. Medical records, including diagnoses and treatments for diabetes were carefully verified. Women that have been diagnosed with type I or type II diabetes mellitus, receiving medicine therapy before conception, as well as those with an early HbA1c level equal to or over 6.5%, a fasting plasma glucose of 7 mmol/L or greater, or a 2-h glucose of 11.1 mmol/L, were regarded as pre-gestational diabetes, and thus excluded from the study population and referred to diabetologists for appropriate management [18,19]. After an overnight fast of at least 8 h, women who met the OGTT criteria, including fasting blood glucose ≥5.1 mmol/L, 1 h blood glucose ≥10.0 mmol/L or 2 h blood glucose ≥8.5 mmol/L were identified as incident GDM [18]. They were assigned blood glucose monitoring, lifestyle management, medical nutrition management and insulin therapy during the follow-up period, if deemed necessary [20]. Finally, a total of 1020 women with GDM were enrolled as cases.

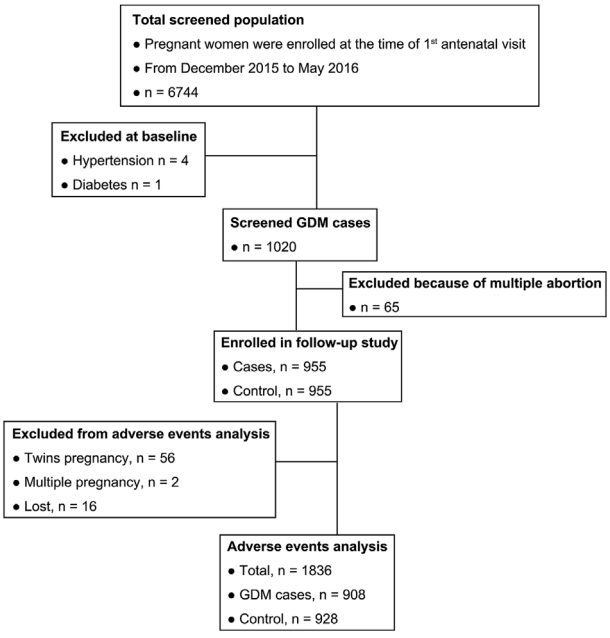


Fig. 1. Flow chart of the participant enrollment, case-control selection and follow-up. GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

To account for potential bias, the pool of eligible controls was a randomly computer-generated group consisting of women with negative GDM tests. Each case was matched with one healthy woman on the basis of age (± 6 months), gestational hypertension, and parity.

For both cases and controls, the exclusion criteria included: (1) OGTT intolerance, pre-gestational diabetes, chronic hypertension, kidney disease, history of multiple abortions and any other significant preexisting chronic medical diseases; (2) history of smoking and excessive alcohol consumption. A total of 65 GDM cases were excluded. There were no significant differences in baseline HbA1c values between enrolled subjects and those excluded.

2.3. Follow-up and adverse events analyses

A total of 955 GDM cases and an equal number of matched controls were followed up until the end of the perinatal period. Electronic medical records of all women were thoroughly reviewed. Names, demographics, clinical and analytical information were derived from electronic medical records at baseline. Assessment of fetal growth and well-being was performed according to the current guidelines [21–24]. During these examinations, the placental location and appearance were recorded. A standard ultrasound examination, including the assessment of gestational age, number of fetuses and location of placenta was performed during the first antenatal visit. A separate ultrasound examination was routinely offered between 18 and 24 weeks for assessment of fetal anatomy, fetal growth, fetal location and amniotic fluid volume, as well as potential suspicion for placental abruption and placenta previa. Verification for the suspicions was performed using a repeat ultrasonography, if needed [23,25]. Most cases of prelabor rupture of membrane (PROM) can be diagnosed on the basis of the patient's history and physical examination [26].

Adverse neonatal events were diagnosed and recorded by physicians according to the current guidelines. Neonates who met the criteria for treatment were diagnosed with neonatal jaundice [13]. Those diagnosed with neonatal pneumonia and other severe clinical symptoms were transferred to specialized departments during the perinatal stage. Outcome analyses were conducted between case and control groups, as well as elevated and normal HbA1c level groups, respectively. Women were excluded from adverse events analyses if they had a multiple pregnancy.

The primary outcome was a composite of adverse fetal events, including umbilical cord abnormality (including cord around neck, cord twining, twist, tying, abnormal attachment, excessively long or short), amniotic fluid abnormality (including polyhydramnios, oligohydramnios and meconium-stained amniotic fluid), placental abnormality (including placental abruption, low-lying placenta, placenta previa, rupture of vasa previa and placenta increta), PROM, as well as a composite of adverse neonatal events, including prenatal death,

macrosomia, low-birthweight infants, Apgar score < 8, neonatal suffocation, RDS, pneumonia, hypoglycemia, jaundice, congenital heart disease and major congenital anomaly.

2.4. Statistical analysis

Controls who met the matching criteria were selected at random using SAS software. Means and proportions of baseline values were calculated for both GDM cases and controls. The significance of differences between groups was tested using one-way ANOVA and Pearson Chi-square tests. Binary logistic regression analysis was used to identify an optimal cutoff which was significantly associated with adverse neonatal events. In the current population, 80.0% of the pregnant women were observed with an early HbA1c equal to or greater than 4.9%. We subsequently calculated HbA1c for 4.9%, 5.0%, and 5.1%, but there were no significant associations with adverse neonatal events, with *p values 0.207, 0.302* and *0.074*, respectively. Thus, our results showed that HbA1c ≥ 5.2% was strongly associated with adverse neonatal events ($p = 0.014$). Binary logistic regression analysis was also used to compute odds ratios (OR) and 95% confidence intervals (CI) to evaluate the associations between GDM cases and normal groups, as well as elevated and normal HbA1c level groups.

The diagnostic accuracy of HbA1c level on adverse events was expressed as the area under the curve (AUC), which was derived from binary logistic regression analysis [27]. Sensitivity and specificity of HbA1c levels were calculated according to standard procedure [28].

Statistical software (SPSS, version 24.0, Inc., Chicago, IL; and SAS, version 9.4, SAS Institute Inc., Cary, NC USA) were used for data processing and analyses. All p values were based on two-tailed tests, and statistical significance was set as α-value of 0.05.

3. Results

A total of 1910 women with available baseline data that was tested and recorded during their first antenatal visit before 14 weeks of gestation, were enrolled in the prospective case-control study. As shown in Table 1, women with GDM had significantly higher bodyweight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c level, blood glucose level, as well as higher frequency of spontaneous abortion, ectopic pregnancy, polycystic ovary syndrome (PCOS), family history of diabetes and hypertension compared with healthy pregnant women.

Subsequently, during the follow-up period, 16 women were ineligible due to delivery in a separate hospital, while 58 women were excluded in outcome analysis due to multiple gestations. A total of 1836 singleton pregnancies (908 GDM cases and 928 controls) with completed data were included in the adverse fetal and neonatal analysis. Among these subjects, early maternal HbA1c levels ranged from 4.0% to 6.4%. Since early maternal HbA1c ≥ 5.2 was most strongly associated with particular adverse events in logistic regression ($p = 0.001$), we categorized these women into normal HbA1c group (4.1–5.1%) and elevated HbA1c group (5.2–6.4%). The baseline characteristic was shown in Table 1. Based on this categorization, a total of 689 women were found to have an early elevated HbA1c level, including 272 women without GDM. However, 189 women (69.5%) without GDM later developed adverse events.

3.1. Frequency and associations of total events

We presented three models for evaluating the associations of adverse fetal and neonatal events between different groups, as shown in Fig. 2: unadjusted (Model 1), adjusted with matching factors (Model 2), adjusted with both matching factors and factors with statistical differences at baseline (Model 3). Of note, the frequency of events between GDM cases and control groups following treatments was not statistically significant ($p \geq 0.084$). However, women with an elevated HbA1c level were more likely to develop adverse events compared with those with a normal HbA1c level ($p \leq 0.006$), in particular, neonatal complications ($p \leq 0.014$).

3.2. Frequency and risks of adverse events associated with GDM and elevated HbA1c level

Women with GDM and an elevated HbA1c level, along with their adjusted risk for each adverse event including OR and relative ratio (RR) were shown in Fig. 3. Risks of umbilical cord abnormality were found in both GDM and elevated HbA1c groups. After treatments, the frequency of other adverse fetal and neonatal events in women with GDM was similar to that of healthy pregnant women ($p \geq 0.114$), with the exception of Apgar Score < 8 (5 min). However, the risks of neonatal RDS (RR = 4.37, 95%CI 1.54–12.35), pneumonia (RR = 2.03, 95%CI 1.24–3.33) and jaundice (RR = 1.49, 95%CI 1.01–2.20) were significantly higher in the elevated HbA1c group.

3.3. Clinical significance of elevated HbA1c levels in predicting RDS

To explore the potential diagnostic significance of early maternal HbA1c level from a clinical perspective, we evaluated the four predictors of neonatal RDS: HbA1c level; combined role of HbA1c levels and gestational hypertension; OGTT; and combined role of OGTT and gestational hypertension, using AUC analysis. As shown in Fig. 4, early maternal HbA1c level is most effective in predicting RDS among the four predictors, with AUC of 0.734. Moreover, HbA1c ≤ 4.9% excluded for RDS. However, both HbA1c level and its combined role with gestational hypertension did not show optimal sensitivity and specificity in the diagnosis of neonatal jaundice and pneumonia.

4. Discussion

In our study, we found that the frequency of women categorized in the GDM, non-GDM, elevated and normal HbA1c groups was 443 (48.8%), 422 (45.5%), 359 (52.1%) and 506 (44.1%), respectively. Following treatments, there were no significant differences shown in adverse neonatal events between GDM cases and healthy pregnant women, however, women with an early elevated HbA1c level were more likely to develop adverse neonatal events compared with those with normal HbA1c level. We further showed that early elevated maternal HbA1c was associated with increased incidences of adverse fetal and neonatal events, including neonatal RDS, pneumonia and jaundice, however, similar associations were not observed between women diagnosed with GDM and normal pregnant women after necessary treatment. Of note, in the early elevated maternal HbA1c group, all 417 women with GDM who had received necessary treatment were still at high risk of these events. Moreover, early maternal HbA1c testing is an effective method for predicting potential incidence of neonatal RDS.

According to current consensus guidelines, interventions to prevent RDS and improve pregnancy outcomes should begin prior to birth, even if the anticipated preterm delivery cannot be prevented [11]. It is also recommended that prenatal corticosteroids be given to women with GDM in order to improve neonate survival and reduce the risk of RDS. However, a meta-analysis showed that dexamethasone, a commonly prescribed corticosteroid, has potential neurotoxicity and can cause brain damage [29]. Therefore, there are currently no generally effective means of preventing adverse outcomes in women with GDM, other than prolonging the gestation period, transfer to a more experienced medical center, or treatment with prenatal corticosteroids [30–33].

The relationship between early maternal blood glucose levels and neonatal RDS remains unclear. A previous study showed that the frequency of RDS was similar in GDM cases and control groups [34], which is consistent with our current study. Similarly, a randomized clinical trial in women with mild GDM showed that the frequency of RDS did not significantly differ between the intervention group and

Table 1
Baseline characteristics stratified according to the GDM diagnose and HbA1c levels n = 1910.

	GDM case (n = 955)	Control (n = 955)	*P*	HbA1c 5.2–6.4% (n = 717)	HbA1c < 5.2% (n = 1193)	*P*
Age, years, mean ± SD	31.0 ± 3.77	31.2 ± 3.79	Match Factor	31.4 ± 3.80	30.8 ± 3.73	0.001
Height, m, mean ± SD	1.61 ± 0.07	1.62 ± 0.05	0.073	1.61 ± 0.05	1.62 ± 0.01	0.144
Weight, kg, mean ± SD	60.6 ± 10.06	58.0 ± 8.11	< 0.001	60.6 ± 10.09	58.3 ± 8.53	< 0.001
BMI, kg/m^2, mean ± SD	23.3 ± 3.46	22.2 ± 2.78	< 0.001	23.3 ± 3.40	22.3 ± 2.97	< 0.001
SBP, mmHg, mean ± SD	111 ± 16.25	109 ± 10.61	0.001	111 ± 14.84	110 ± 12.74	0.117
DBP, mmHg, mean ± SD	74 ± 24.88	72 ± 8.81	0.006	74 ± 28.30	73 ± 9.42	0.125
Pregnancy History						
Multipara, n (%)	396 (41.5%)	396 (41.5%)	Match Factor	307 (42.8%)	485 (40.7%)	0.385
Preterm Labor, n (%)	11 (1.2%)	7 (0.7%)	0.346	13 (1.8%)	5 (0.4%)	0.002
Caesarean, n (%)	120 (12.7%)	112 (12.7%)	0.587	89 (12.4%)	143 (12.0%)	0.782
Spontaneous Abortion, n (%)	187 (19.7%)	89 (9.4%)	< 0.001	118 (16.5%)	158 (13.2%)	0.053
Induced Abortion, n (%)	213 (22.3%)	202 (21.4%)	0.506	159 (22.2%)	256 (21.5%)	0.713
Fetal Death, n (%)	7 (0.7%)	2 (0.2%)	0.095	7 (1.0%)	2 (0.2%)	0.031
Ectopic Pregnancy, n (%)	18 (1.9%)	0 (0.0%)	< 0.001	10 (1.4%)	8 (0.7%)	0.113
Previous History						
PCOS, n (%)	18 (1.9%)	7 (0.7%)	0.028	12 (1.7%)	13 (1.1%)	0.277
Hyperthyroidism, n (%)	5 (0.5%)	3 (0.3%)	0.726	1 (0.1%)	7 (0.6%)	0.271
Cardiovascular Disease, n (%)	4 (0.4%)	1 (0.1%)	0.374	3 (0.4%)	2 (0.2%)	0.37
Other Metabolic Disease, n (%)	11 (1.2%)	3 (0.3%)	0.056	9 (1.3%)	5 (0.4%)	0.038
Family History						
Diabetes, n (%)	137 (21.4%)	66 (7.0%)	< 0.001	108 (15.1%)	95 (8.0%)	< 0.001
Hypertension, n (%)	290 (30.6%)	224 (23.7%)	0.001	228 (31.8%)	286 (24.0%)	< 0.001
Blood Glucose						
HbA1c, %, mean ± SD	5.1 ± 0.30	5.0 ± 0.25	< 0.001	5.4 ± 0.18	4.9 ± 0.19	< 0.001
FBG, mmol/L, mean ± SD	4.7 ± 0.48	4.6 ± 0.34	< 0.001	4.8 ± 0.46	4.6 ± 0.39	< 0.001
PBG, mmol/L, mean ± SD	6.1 ± 1.27	6.3 ± 1.25	0.508	6.2 ± 1.39	6.0 ± 1.16	0.025
75 g OGTT						
Fasting, mmol/L, mean ± SD	4.9 ± 0.55	4.4 ± 0.35	< 0.001	4.8 ± 0.53	4.6 ± 0.42	< 0.001
1 h, mmol/L, mean ± SD	9.7 ± 1.49	7.4 ± 1.35	< 0.001	9.0 ± 1.81	8.2 ± 1.80	< 0.001
2 h, mmol/L, mean ± SD	8.3 ± 1.33	6.4 ± 0.99	< 0.001	7.7 ± 1.59	7.1 ± 1.45	< 0.001

p = 0.05.
BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PBG, postprandial blood glucose; PCOS, polycystic ovary syndrome; SBP, Systolic Blood Pressure.

standard prenatal care group (1.9% and 2.9%, respectively; RR, 0.66; 95% CI, 0.26 to 1.67; $p = 0.33$) [9]. In a separate study, HbA1c level and the risk of RDS was demonstrated to have no statistical significance in the type I ($p = 0.048$) and the type II diabetes mellitus group ($p = 0.036$) [35]. In contrast, our present study demonstrated that women with an early elevated HbA1c level had a significantly higher risk of developing adverse neonatal outcomes, after adjusting for the confounder of pre-existing diabetes.

Previous studies have suggested that macrosomia belonging to diabetic mothers have a higher risk of severe hyperbilirubinemia compared with non-diabetic mothers [36,37]. In addition, a study showed that neonatal jaundice was more prevalent in women diagnosed with GDM at < 12 weeks of gestation compared to those that were diagnosed later on ($p < 0.001$) [38]. Furthermore, a study in Chinese women showed that the frequency of neonatal jaundice and pneumonia did not significantly different between GDM treatment

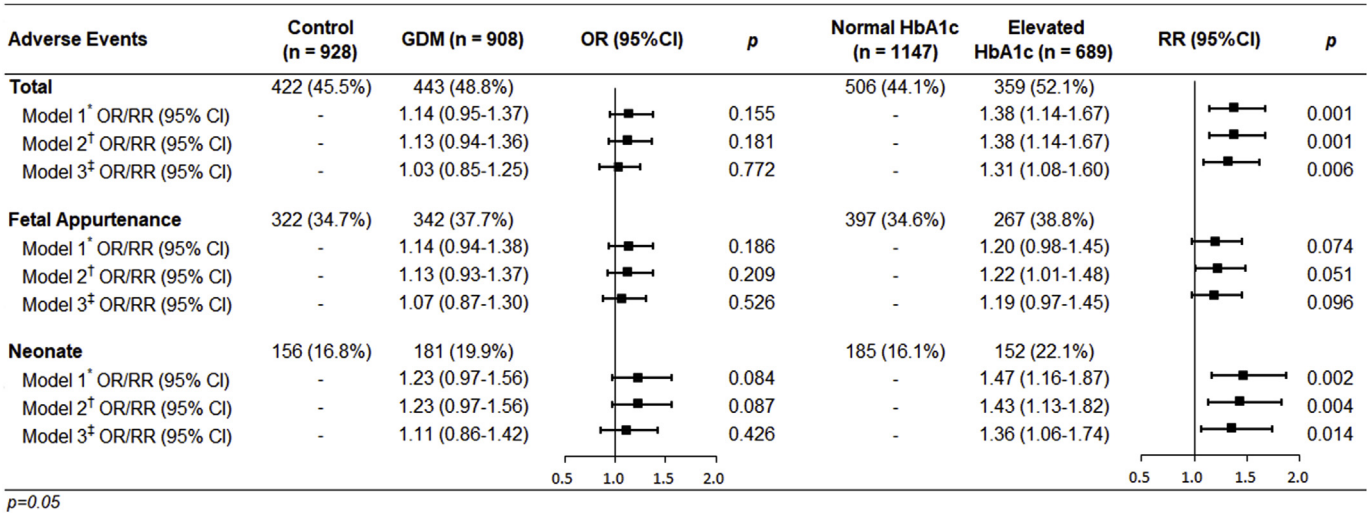
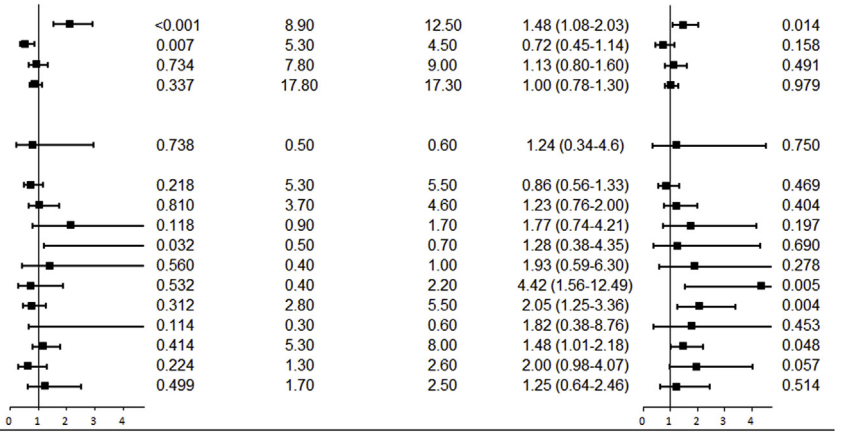


Fig. 2. Frequency and risk of total fetal and neonatal events (n = 1836).
* Model 1: unadjusted; † Model 2: adjusted with age, parity and gestational hypertension; ‡ Model 3: adjusted with age, BMI, SBP, DBP, parity, gestational hypertension, history of preterm labor, caesarean, spontaneous abortion, fetal death, ectopic pregnancy, PCOS, other metabolic disease as well as family history of diabetes and hypertension. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; OR, odds ratio; PCOS, polycystic ovary syndrome; RR, risk ratio; SBP, systolic blood pressure.

Adverse Events	Frequency in controls (%, n = 928)	Frequency in GDM cases (%, n = 908)	OR (95% CI)	OR (95% CI)	p	Frequency in normal HbA1c group (%, n = 1147)	Frequency in elevated HbA1c group (%, n = 689)	RR (95% CI)	RR (95% CI)	p
Fetal Appurtenance										
Umbilical Cord Abnormality	6.90	13.70	2.11 (1.52-2.93)		<0.001	8.90	12.50	1.48 (1.08-2.03)		0.014
Amniotic Fluid Abnormality	5.90	4.10	0.53 (0.34-0.84)		0.007	5.30	4.50	0.72 (0.45-1.14)		0.158
Placental Abnormality	8.50	8.00	0.94 (0.67-1.33)		0.734	7.80	9.00	1.13 (0.80-1.60)		0.491
PROM	18.10	17.10	0.88 (0.69-1.14)		0.337	17.80	17.30	1.00 (0.78-1.30)		0.979
Neonate										
Prenatal Death	0.50	0.60	0.80 (0.22-2.96)		0.738	0.50	0.60	1.24 (0.34-4.6)		0.750
Birth Weight										
⩾4000 g	5.50	5.30	0.76 (0.50-1.17)		0.218	5.30	5.50	0.86 (0.56-1.33)		0.469
<2500 g	4.00	4.20	1.06 (0.65-1.72)		0.810	3.70	4.60	1.23 (0.76-2.00)		0.404
Apgar Score <8 (1 mins)	0.60	1.80	2.18 (0.82-5.79)		0.118	0.90	1.70	1.77 (0.74-4.21)		0.197
Apgar Score <8 (5 mins)	0.10	1.10	9.75 (1.22-78.12)		0.032	0.50	0.70	1.28 (0.38-4.35)		0.690
Suffocation	0.40	0.90	1.45 (0.41-5.12)		0.560	0.40	1.00	1.93 (0.59-6.30)		0.278
RDS	1.10	1.10	0.74 (0.29-1.89)		0.532	0.40	2.20	4.42 (1.56-12.49)		0.005
Pneumonia Transferred	3.30	4.30	0.77 (0.47-1.27)		0.312	2.80	5.50	2.05 (1.25-3.36)		0.004
Hypoglycemia	0.10	0.70	5.70 (0.66-49.33)		0.114	0.30	0.60	1.82 (0.38-8.76)		0.453
Jaundice	5.60	7.00	1.18 (0.80-1.75)		0.414	5.30	8.00	1.48 (1.01-2.18)		0.048
Congenital Heart Disease	2.00	1.50	0.64 (0.31-1.32)		0.224	1.30	2.60	2.00 (0.98-4.07)		0.057
Major Congenital Anomaly	1.60	2.40	1.27 (0.635-2.54)		0.499	1.70	2.50	1.25 (0.64-2.46)		0.514



p=0.05

Fig. 3. Adjusted risk of adverse fetal and neonatal events associated with GDM and early elevated maternal HbA1c * (n = 1836).
* adjusted with age, BMI, SBP, DBP, parity, gestational hypertension, history of preterm labor, caesarean, spontaneous abortion, fetal death, ectopic pregnancy, PCOS, other metabolic disease as well as family history of diabetes and hypertension. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; OR, odds ratio; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PROM, prelabor rupture of fetal membranes; RDS, respiratory distress syndrome; RR, risk ratio; SBP, systolic blood pressure.

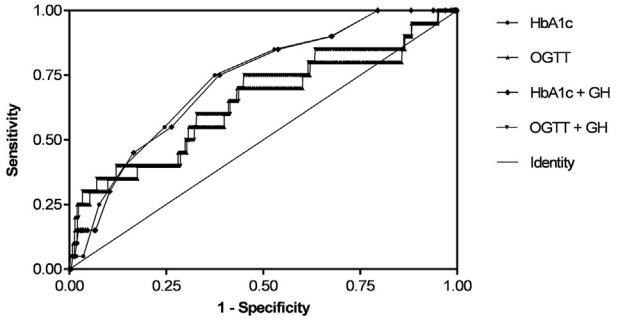


Fig. 4. ROC plots of the performance of early maternal HbA1c in identifying potential RDS
AUC of HbA1c = 0.734 (0.636–0.831); AUC of the combined role of HbA1c and gestational hypertension = 0.729 (0.629–0.828); AUC of OGTT = 0.635 (0.493–0.776); AUC of the combined role of OGTT and gestational hypertension = 0.660 (0.525–0.795). AUC, area under the curve; GH, gestational hypertension; OGTT, oral glucose tolerance test; RDS, respiratory distress syndrome; ROC plots, receiver operating characteristic plots.

group and control group ($p = 0.500$ and 0.125, respectively) [39], which is consistent with our current study. Women with GDM have a higher risk of infectious diseases, however, the relationship between early maternal glucose and neonatal pneumonia remains unclear.

Recent studies have showed that early maternal HbA1c ≥ 5.9% could detect all women with unknown diabetes and subsequently identified women with an increased risk of adverse pregnancy outcomes [40,41]. This discrepancy in HbA1c level can be partly attributed to the differences in ethnic origin of the study populations [42,43]. In addition, the previously reported upper limit of early maternal HbA1c among different populations range from 5.5 to 5.7% [44–47]. However, the current study was conducted exclusively within a Chinese population. More importantly, the cutoff point of 5.2% was established to identify potential neonatal RDS, pneumonia and jaundice, whereas the previous studies mainly aimed to identify adverse pregnancy outcomes [42,43]. However, there is generally no risk threshold for most fetal and neonatal complications within a Chinese population.

According to the current guidelines, the criteria for testing for diabetes or GDM are different, that is, patients diagnosed with fasting blood glucose level should be equal to or greater than 7.0 mmol/L or 5.1 mmol/L, respectively [18]. Pregnancy in women with normal glucose metabolism is characterized by a lower level of fasting blood glucose than in the non-pregnant state, which means that the glycemic targets in pregnancy are stricter than in non-pregnant individuals [20]. Similarly, as an integrated measure of glucose, HbA1c level falls during normal pregnancy because of the physiological increase in red blood cell turnover in line with a decrease in fasting blood glucose level [48]. In addition, it has been demonstrated that risk of adverse maternal, fetal, and neonatal outcomes could increase as a function of maternal glycemia at 24–28 weeks of gestation, within ranges that are considered normal for pregnancy [1]. Therefore, establishing a cutoff for HbA1c level for particular events is critical.

Moreover, it has been reported that there is a decrease in HbA1c level from the first to the second trimester, which then tended to increase in the third trimester [49]. In the current study, we examined HbA1c level in the first trimester rather than the second or third trimester, since by then any adverse effects should already be evident at these delayed intervals. However, HbA1c level at the pre-diabetic range is only weakly associated with underlying pathophysiological components of impaired glucose metabolism, including impaired insulin action and β-cell dysfunction [50], suggesting that the limitations of HbA1c level testing needs to be considered.

Our study showed that even when necessary treatments had been received, women with both GDM and an early elevated HbA1c level have a higher risk of neonatal complications. After treatment, the frequency of most adverse fetal and neonatal events in women with GDM was consistent to that of healthy pregnant women, while in contrast, women with an early elevated HbA1c level had significantly higher risks of neonatal RDS, pneumonia and jaundice. Early maternal HbA1c testing provides an optimal opportunity for preventing particular adverse neonatal events. Thus, the systematic application of early maternal HbA1c testing should be routinely used during the initial antenatal examination in order to identify pregnant women who are at risk of neonatal RDS, pneumonia and jaundice, which would allow timely interventions and prevention during early pregnancy.

5. Limitations

The current study is prospectively conducted in a single hospital. Due to the nested case-control design, there might be a possibility of

selection bias. Therefore, the conclusions in this study should be verified in future randomized clinical trials.

6. Conclusions

Women with an early elevated HbA1c level (5.2%–6.4%) have a higher risk of neonatal RDS, pneumonia and jaundice. Following treatments, the frequency of almost all adverse fetal and neonatal events in women with GDM were similar to that of healthy pregnant women. Moreover, early maternal HbA1c testing can be used as an auxiliary method for predicting potential RDS. This assessment should be routinely used during early antenatal examinations in order to decrease the potential risk of adverse neonatal events.

Conflicts of interest

None declared.

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Jue Li conceived and designed the study. Han Yu designed the questionnaire, collected the data, performed statistical analysis and drafted the manuscript. Yeshaswi Shrestha, Yongjia Hu, Yuan Ma, Longbing Ren helped to collect the data. Jun Zhang acquired the data. All authors made final approval of the version to be submitted.

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