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Increased levels of glycosylated hemoglobin, microalbuminuria and serum cystatin C predict adverse outcomes in high-risk pregnancies with gestational diabetes mellitus

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Abstract. In the present study, the predictive value of glycosylated hemoglobin (HbA1c), microalbuminuria (24 h mAlb) and serum cystatin C (Cys-C) levels on the outcome of pregnancy in patients with gestational diabetes mellitus (GDM) was investigated. Samples of 144 females with GDM and 117 normal pregnant females as controls were selected for retrospective analysis. The following parameters were compared between the two groups: Levels of HbA1c, Cys-C and 24 h mAlb, maternal pregnancy outcome and adverse pregnancy rate. The predictive value of elevated 24 h mAlb, HbA1c and Cys-C regarding an adverse pregnancy outcome was then determined. Cys-C, 24 h mAlb and HbA1c levels in the GDM group were significantly higher than those in the control group (P<0.001). The adverse pregnancy rate in the GDM group was significantly higher than that in the control group (40.97 vs. 16.24%; P<0.001). Logistic regression and receiver operating characteristics (ROC) analyses indicated that, in subjects with GDM, HbA1c, Cys-C and 24 h mAlb levels were closely associated with adverse pregnancy outcomes (P<0.050) and may be considered as predictors for an adverse pregnancy outcome (risk ratio >1). Linear correlation analyses indicated that HbA1c, Cys-C and 24 h mAlb were negatively correlated with the neonatal Apgar scores (r=-0.509, -0.954 and -0.954, respectively; P<0.001). According to ROC analysis, the combined predictive sensitivity of HbAlc, Cys-C and 24 h mAlb for adverse pregnancy outcome in patients with GDM was 96.49% and the specificity was 77.19%. The increase in HbAlc, Cys-C and 24 h mAlb levels is expected to be an effective predictor of adverse pregnancy outcomes in high-risk pregnant women.

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Key words: glycated hemoglobin, microalbuminuria, serum cystatin C, gestational diabetes mellitus, pregnancy outcome

Introduction

Gestational diabetes mellitus (GDM) is clinically classified as a high-risk pregnancy condition (1). In recent years, the incidence of GDM is increasing with continuous changes in living standards and eating habits (2). It has been estimated that 1 out of 15 pregnant females is susceptible to GDM, and in developed countries, including the US and the UK, the incidence of GDM exceeds 10%. The uterus of patients with GDM has a high-glucose environment, which may exert long-term effects on the mother and fetus (3). GDM may greatly increase the incidence of complications during pregnancy, including polyhydramnios, eclampsia and premature delivery. More seriously, it may lead to abortion (4). In addition, the probability of fetal malformation and developmental limitation is markedly increased in patients with GDM. If the fetus remains in a high-glucose environment during pregnancy, it is prone to developing respiratory distress syndrome and hypoglycemia once delivered, which may be life-threatening to the infant (5). According to a survey, ~24.84% of females with GDM developed GDM-associated diseases, including respiratory distress syndrome, organ dysplasia, following childbirth (6). Owing to the high incidence of GDM and high risk associated with it, the present study investigated methods which may facilitate effective clinical diagnosis and treatment of GDM. To date, no breakthrough has been achieved with this regard. Therefore, an increasing number of studies performed worldwide focus on the identification of effective indicators for pregnancy outcomes in patients with GDM, which may allow for the prevention and treatment of GDM. Studies have indicated that glycosylated hemoglobin (HbA1c) and urinary microalbuminuria (24 h mAlb) are closely associated with GDM (7-9), while serum cystatin C (Cys-C) is a highly sensitive indicator of renal impairment (10). In the present study, it was hypothesized that Cys-C may also be abnormally elevated in patients with GDM, and that detection of HbA1c, 24 h mAlb and Cys-C may be an effective predictor of pregnancy outcomes in patients with GDM. Therefore, a retrospective analysis of patients with GDM was conducted to provide support for future clinicians in the diagnosis and treatment of adverse pregnancy in patients with GDM.

Materials and methods

General information. A total of 144 pregnant females with GDM admitted to the Department of Obstetrics, Qingpu

Branch, Zhongshan Hospital Affiliated to Fudan University (Shanghai, China) between August 2016 and September 2017, were selected for retrospective analysis. Their age ranged from 22 to 35 years, with an average of 27.12±4.93 years. A further 117 cases of normal pregnancy (age, 22-34 years; average age, 26.83±4.62 years) were selected as the control group. The experiment was approved by the Ethics Committee of Qingpu Branch, Zhongshan Hospital Affiliated to Fudan University (Shanghai, China) and all subjects provided written informed consent.

Inclusion and exclusion criteria. Criteria for inclusion were as follows: i) Pregnant women diagnosed with GDM via oral glucose tolerance test, in line with the 2016 GDM diagnostic guidelines (11); ii) Blood glucose <7.0 mmol/l; iii) delivery at the Zhongshan Hospital Affiliated to Fudan University; and iv) complete medical data. The exclusion criteria were as follows: i) Family history of genetic diabetes; ii) presence of a tumor; iii) mental illness; iv) cardio-cerebral vascular disease; v) severe liver and kidney dysfunction; vi) organ failure; vii) fetal congenital malformation diagnosed by B-ultrasound; viii) patients who were long-term bedridden; and ix) patients transferred from another hospital.

Collection of biological fluids and measurement of biomarkers. Pregnant women with GDM were classified as the GDM group and normal pregnant women were categorized as the control group. The 24-h urine samples were collected from 7 to 7 am the next day, and 10 ml urine per sample was used. Following centrifugation for 5 min at 2,432 x g (20˚C), the supernatant of the urine was obtained, and the 24-h urine 24 h mAlb levels of the two groups were determined via the biuret method. In the morning, 5 ml fasting venous blood was drawn from patients and centrifuged for 10 min at 2,432 x g (20˚C). The serum in the supernatant was divided into two portions that were stored in a -80˚C refrigerator for testing. One portion was used to detect HbA1c levels with an automatic biochemical analyzer (AU5800; Beckman Coulter), while the other portion was used to detect Cys-C levels via latex-enhanced immunoturbidimetric assay according to manufacturer's protocol (cat. no. UFWD0121; Shanghai Junrui Biotechnology Co., Ltd.) (12).

Observation indicators. The following information was collected: Maternal clinical information including age, body weight and gestational age; HbA1c level; Cys-C level; 24 h mAlb level; pregnancy outcome and adverse pregnancy rate; preterm birth (28-37 weeks pregnancy); premature rupture of membranes (progressive uterine cervix decline before delivery; cervical tube disappearance and fetal malposition decline); polyhydramnios (largest pocket depth of abdominal by ultrasound prior to delivery ≥8 cm or amniotic fluid volume after delivery >2,000 ml; fetal distress (average 10-min fetal heart rate >180 or <120 beats/min); abnormal fetal development (body weight <2,500 g for developmental obstruction, weight >4,000 g for a huge infant). The correlations of HbA1c, Cys-C and 24 h mAlb with adverse pregnancy outcomes, including adverse pregnancy rates and neonatal Apgar scores [according to 2016 Newborn Apgar scoring standard (13)] were then determined.

Statistical analysis. The data were analyzed and processed using the SPSS 22.0 statistical package (IBM Corp.). Enumeration data, including the place of residence, lifestyle habits and adverse pregnancies, were expressed as rates. Comparisons between groups were performed using the chi-squared test. Continuous variables, including age, body weight and HbA_{1c} levels were expressed as the mean ± standard deviation. The Independent Samples t-test was used for comparison of means. Correlation between HbAlc, Cys-C, mAlb and neonatal Apgar scores was analyzed by Pearson correlation coefficient; Logistic regression analysis was used to correlate HbAlc, Cys-C, mAlb and adverse pregnancy outcomes. Predictive values were analyzed using receiver operating characteristic (ROC) curves. P<0.05 was considered to indicate a statistically signficant difference.

Results

Comparison of clinical data. There was no difference in age, weight, gestational age, blood routine examination and the place of residence between the two groups (P>0.05), suggesting that the two groups were comparable (Table I).

Comparison of HbA1c, Cys-C and 24 h mAlb levels. The level of HbA1c of the GDM group (8.56±0.42%) was significantly higher than that in the control group (6.57±0.22%; P<0.001; Fig. 1). The serum levels of Cys-C in the GDM group (1.53±0.40 mg/l) were significantly higher than those in the control group (0.92±0.17 mg/l; P<0.001; Fig. 2). Furthermore, the levels of 24 h mAlb in the GDM group (21.24±5.59 mg/l) were significantly higher than those in the control group (16.69±4.27 mg/l; P<0.001; Fig. 3).

Comparison of adverse pregnancy rates. In the GDM group, the premature delivery rate was 9.03%, the premature membrane rupture rate was 10.42%, the polyhydramnios rate was 5.56%, the fetal distress rate was 9.03% and the abnormal fetal development rate was 6.94%. In the control group, the premature delivery rate was 5.13%, the premature membrane rupture rate was 4.27%, the polyhydramnios rate was 2.56%, the fetal distress rate was 1.71% and the abnormal fetal developmental rate was 2.56%. The rate of adverse pregnancy in the GDM group (40.97%) was significantly higher than that in the control group (16.24%; P<0.001; Table II).

Association of HbA1c, Cys-C and 24 h mAlb with adverse pregnancy outcomes. Logistic regression analysis indicated that in maternal patients with GDM, but not in healthy pregnant women, HbA1c, Cys-C and 24 h mAlb were closely associated with adverse pregnancy outcomes (P<0.050) and were risk factors leading to adverse pregnancy outcomes in GDM (Table III).

Correlation between HbA_{1c}, Cys-C, 24 h mAlb and neonatal Apgar score. The Apgar score of the neonates in the GDM group was 7.12±1.07. Linear correlation analysis indicated that HbA1c, Cys-C and 24 h mAlb were negatively correlated with the neonatal Apgar score (r=-0.509, -0.678 and -0.733, respectively; P<0.001; Figs. 4-6).

Table I. Comparison of general data between the two groups.

Parameter	GDM group (n=144)	Normal group (n=117)	t or χ^2	P-value
Age (years)	27.12±4.93	26.83±4.62	0.486	0.627
Body weight (kg)	61.24±6.24	60.55±6.51	0.871	0.384
Gestational week	38.62±5.21	39.27±5.84	0.949	0.343
WBC ($x10^9$/l)	16.24±5.04	16.81±4.86	0.923	0.357
RBC ($x10^{12}$/l)	6.28±2.07	5.94±2.44	1.218	0.224
PLT ($x10^9$/l)	187.24±34.51	194.53±29.85	1.802	0.072
Place of residence			0.880	0.348
Town	81 (56.25)	59 (50.43)		
Rural area	63 (43.75)	58 (49.57)		
Primipara			0.312	0.576
Yes	131 (90.97)	104 (88.89)		
No	13 (9.03)	13 (11.11)		

Values are expressed as n (%) or the mean ± standard deviation. WBC, white blood cells; RBC, red blood cells; PLT, platelets; GDM, gestational diabetes mellitus.

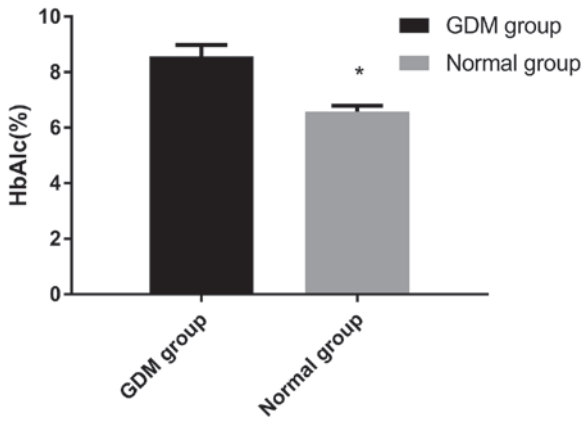

Figure 1. Comparison of HbA1c levels between the two groups. HbA1c levels were significantly higher in the GDM group than those in the control group. *P<0.001 vs. GDM group. HbA1c, glycated hemoglobin; GDM, gestational diabetes mellitus.

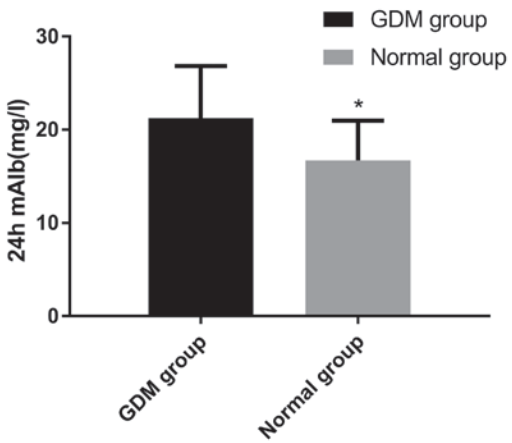

Figure 2. Comparison of Cys-C levels between the two groups. Cys-C levels were significantly higher in the GDM group than those in the control group. *P<0.001 vs. GDM group. Cys-C, cystatin C; GDM, gestational diabetes mellitus.

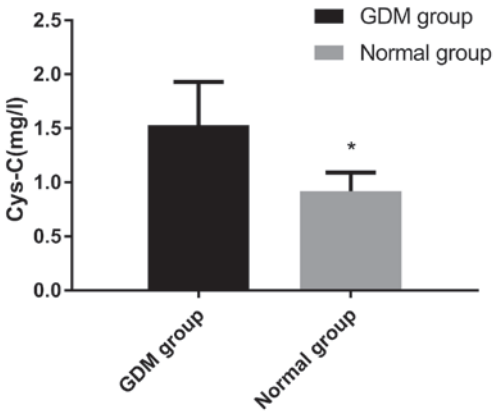

Figure 3. Comparison of 24 h mAlb levels between the two groups. The 24 h mAlb levels were significantly higher in the GDM group than those in the control group. *P<0.001 vs. GDM group. 24 h mAlb, microalbuminuria; GDM, gestational diabetes mellitus.

Predictive value of HbAlc, Cys-C and 24 h mAlb regarding adverse pregnancy outcomes for patients with GDM. Binary logistic analysis was performed using HbAlc, Cys-C, and 24 h mAlb as three independent variables to obtain joint predictive factors, using the following formula: Log(P) value = 1.626 + 0.051 x HbAl + 0.426 x Cys-C + 0.623 x 24 h mAlb. According to ROC analysis, the predictive sensitivity of HbAlc, Cys-C and 24 h mAlb for adverse pregnancy outcome was calculated to be 96.49% and the specificity was calculated to be 77.19% (Fig. 7; Table IV).

Discussion

Pregnancy is a unique circumstance under which the female body undergoes certain physiological changes. Alterations in glucose metabolism are among the most significant physiological changes that occur during this process (14). The fasting blood glucose levels of the mother are generally

Table II. Comparison of adverse pregnancy rates between the two groups.

Item	GDM group (n=144)	Normal group (n=117)	χ^2	P-value
Premature birth	13 (9.03)	6 (5.13)	1.454	0.228
Premature rupture of membranes	15 (10.42)	5 (4.27)	3.443	0.064
Excessive amniotic fluid	8 (5.56)	3 (2.56)	1.431	0.232
Fetal intrauterine distress	13 (9.03)	2 (1.71)	6.383	0.012
Abnormal fetal development	10 (6.94)	3 (2.56)	2.617	0.106
Overall adverse pregnancy rate (%)	40.97	16.24	18.841	<0.001

Values are expressed as n (%) unless otherwise specified. GDM, gestational diabetes mellitus.

Table III. Correlation analysis between HbA1c, Cys-C and 24 h mAlb and adverse pregnancy rate in patients with GDM.

Factor	Reference range	Hazards ratio	SE	B	95% CI	P-value
HbAlc	4-6%	0.247	0.468	12.314	1.369-3.816	0.002
Cys-C	0.51-1.09 mg/dl	0.670	0.191	8.723	1.093-2.473	0.017
24 h mAlb	<150 mg/24 h	0.229	0.555	6.942	1.045-2.185	0.028

SE, standard error; HbA1c, glycated hemoglobin; CI, confidence interval; Cys-C, cystatin C; 24 h mAlb, microalbuminuria.

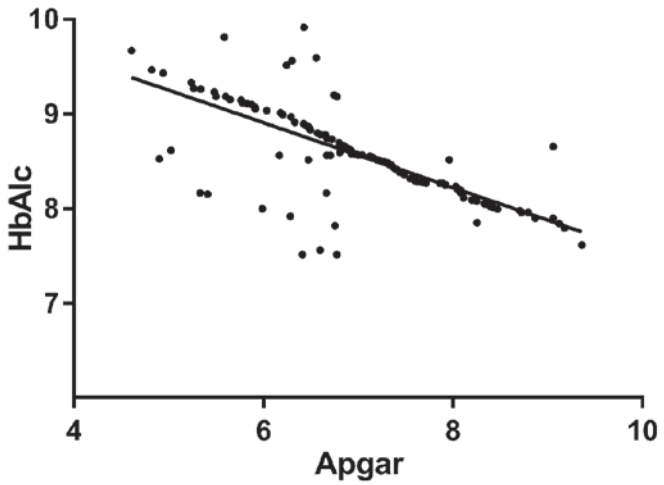

Figure 4. Correlation of HbA1c with neonatal Apgar scores in patients with GDM. Linear correlation analysis indicated that the level of HbA1c was negatively correlated with the neonatal Apgar scores (r=-0.509; P<0.001). HbA1c, glycated hemoglobin.

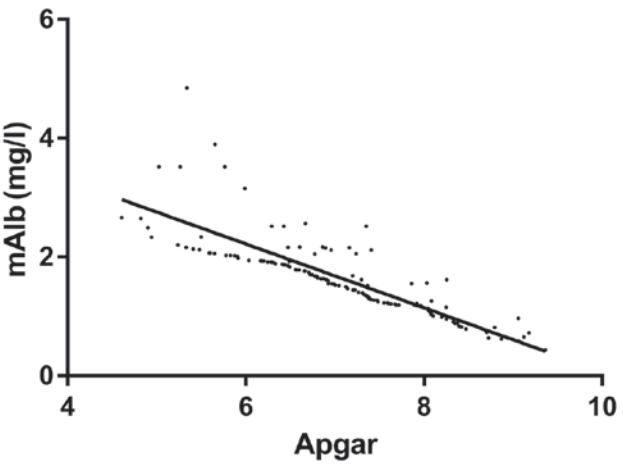

Figure 5. Correlation of 24 h mAlb with neonatal Apgar score. Linear correlation analysis indicated a negative correlation between 24 h mAlb and neonatal Apgar scores (r=-0.954; P<0.001). 24 h mAlb, microalbuminuria.

reduced during pregnancy, and this is associated with a high incidence of GDM (15). The primary reason for the decrease in maternal blood glucose is that the fetus consumes a large amount of sugar during development, and insulin accelerates the release of glucose into the blood for metabolization, which then also decreases the blood sugar levels (16). It has been indicated that blood glucose metabolism in pregnant females is significantly lower compared with that in non-pregnant females. The key factor affecting maternal blood glucose is insulin, the sensitivity to which is significantly reduced during pregnancy (17). Therefore, in order to maintain normal functioning of the maternal body, accelerated secretion of insulin in pregnant females must be regulated. In pregnant females with impaired insulin secretion, smooth acceleration of insulin secretion may not be possible, leading to abnormal glucose metabolism and onset of GDM (18,19). GDM is a high-risk disease during pregnancy. If the optimal treatment time is missed, GDM causes functional and environmental changes affecting fetal blood sugar metabolism, leading to a variety of adverse pregnancy outcomes (20). For GDM, clinical treatment is essentially according to the principle 'early detection, early treatment'. At present, HbA1c remains the gold standard for monitoring blood sugar function. The formation rate of HbA1c, which is produced by the interaction of hemoglobin and carbohydrates, and the blood glucose concentration are positively correlated (20,21). Therefore, detection of HbA1c

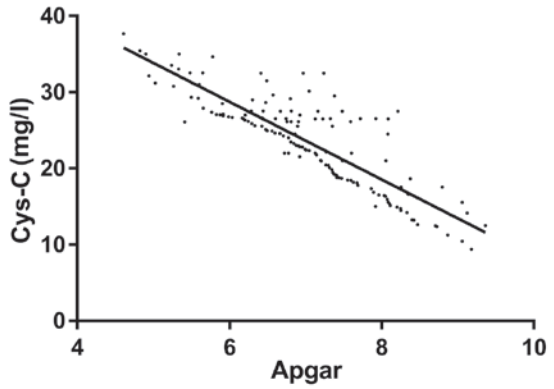

Figure 6. Correlation between serum Cys-C and neonatal Apgar scores. Linear correlation analysis indicated that the level of Cys-C was negatively correlated with the neonatal Apgar score (r=-0.954; P<0.001). Cys-C, cystatin C.

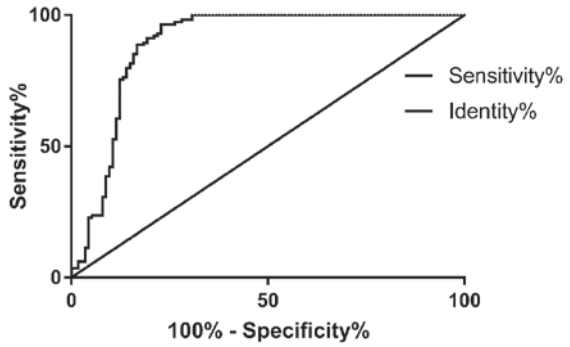

Figure 7. Predictive value of maternal HbAlc, Cys-C and 24 h mAlb for adverse pregnancy outcomes in patients with GDM. According to logistic regression analysis, the combined predictive sensitivity of HbAlc, Cys-C and 24 h mAlb in pregnant females for adverse pregnancy outcomes was 96.49% and the specificity was 77.19%.

Table IV. Predictive value of maternal HbAlc, Cys-C and 24 h mAlb combined for adverse pregnancy outcomes.

Variable	Numerical value
AUC	0.891
Standard deviation	0.024
95% CI	0.843-0.939
Cut-off (ng/ml)	1.249
Sensitivity (%)	96.49
Specificity (%)	77.19
P-value	<0.001

HbA1c, glycated hemoglobin; Cys-C, cystatin C; CI, confidence interval; 24 h mAlb, microalbuminuria; AUC, area under the receiver operating characteristic curve.

in the clinic may reflect simple blood glucose levels during pregnancy and facilitate the identification of the development of GDM. 24 h mAlb and Cys-C are sensitive indicators of renal injury and serve as important reference points for glomerular microangiopathy in females with GDM (22). To date, only a few associated reference studies between GDM pregnancy outcomes and HbA1c, Cys-C and 24 h mAlb have been performed (23,24). Therefore, the present study aimed to establish maternal HbA1c, Cys-C and 24 h mAlb as predictors of pregnancy outcomes in subjects with GDM.

The results of the present study demonstrated that the levels of HbA1c, Cys-C and 24 h mAlb in the GDM group were significantly higher than those in the control group, which is consistent with the results of Chawla and Malik (25). The significantly increased level of 24 h mAlb in the GDM group was attributed to an increase in blood volume, renal blood flow and the glomerular filtration rate during pregnancy, which markedly increased urinary protein excretion. In addition, a high-glucose environment is always present in patients with GDM. In these subjects, endothelial cells promote the release of vasoactive substances, thus altering plasma protein filtration in the glomerular basement membrane. They exhibited a large amount of protein in the blood circulation which were leaked into the urine. Females with normal pregnancies did not exhibit a significant increase in 24 h mAlb, whereas patients with GDM had a significantly increased 24 h mAlb expression, suggesting that 24 h mAlb may be used as an effective indicator of glomerular damage. Cys-C is a low-molecular, non-glycosylated protein, consisting of 122 amino acids residues, which is cleared by the kidneys, resulting in low levels in normal individuals (26). However, impaired kidney function reduces the clearance rate of Cys-C, resulting in high plasma levels. A mother and her fetus are intimately connected during pregnancy, and any abnormal condition in the mother influences the fetus to varying degrees. In the present study, the adverse pregnancy rate in the GDM group was significantly higher than that in the control group, and it was suggested that HbA1c, Cys-C and 24 h mAlb may be used as indicators for predicting pregnancy outcomes in pregnant females. The major cause for the association of HbA1c, Cys-C and 24 h mAlb with the pregnancy outcome is presumed to be blood glucose. Abnormal glucose metabolism in the mother and high insulin levels in the long-term high-glucose fetal environment activate the amino acid transfer system, which greatly increases the synthetic ability of proteins. However, fat disintegration is reduced, resulting in the accumulation of a large amount of fat and glucose in the fetal tissues, leading to various developmental dysfunctions in the neonate. At the same time, due to the high permeability of the uterus between the mother and fetus, their blood sugar levels may increase with the mother (27). Stimulation by high glucose destroys blood vessel walls, causing spasms. Capillary stenosis in the placenta causes narrowing of the vascular lumen, thereby considerably reducing hemodynamics and causing a shortage of blood supply to the fetus, which may lead to several fetal issues. In the present study, HbA1c, Cys-C and 24 h mAlb were negatively correlated with the neonatal Apgar scores in patients with GDM, suggesting that combined HbAlc, Cys-C and 24 h mAlb reading can be used to predict the outcome of delivery in GMD patients. ROC analysis indicated that HbAlc, Cys-C and 24 h mAlb levels of pregnant females with GDM have a relatively high sensitivity and specificity for predicting adverse pregnancy outcomes, suggesting that future clinical trials may determine pregnancy outcomes by detecting the levels of these indicators to provide protective intervention as early as possible.

Of note, the present study does contain certain limitations. Effective data analyses of other types of high-risk pregnancies was not possible, as the experimental population was relatively small. The age range of the study subjects was relatively narrow, and it may not be excluded that HbAlc, Cys-C and 24 h mAlb are different in pregnant females of different ages and geographical regions. In addition, due to the short experimental period, it was impossible to determine the association of HbAlc, Cys-C and 24 h mAlb with the prognosis of GDM-associated health conditions in the mothers after pregnancy. In the future, a more detailed follow-up of the subjects will be performed and the number of subjects will be increased to obtain the best possible experimental results.

In conclusion, the present study indicated that HbA1c, Cys-C and 24 h mAlb are elevated in females with GDM, and may be effective indicators of adverse outcomes of high-risk pregnancies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contribution

HJ conceived and designed the study and interpreted the results, analyzed the data, prepared the figures, drafted, edited and revised manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Qingpu Branch, Zhongshan Hospital Affiliated to Fudan University (Shanghai, China) and all subjects provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The author declare that she has no competing interests.

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