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Plasma Lnc-UCA1/miR-138 axis as a potential biomarker for gestational diabetes mellitus and neonatal prognosis

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ABSTRACT

Objectives: This study aimed to explore the correlations of Lnc-UCA1/miR-138 axis with gestational diabetes mellitus (GDM) risk and neonatal prognosis.

Material and methods: First, the blood samples from sixty GDM patients and 60 healthy pregnant women were collected to detect the change of Lnc-UCA1/miR-138 axis by using real-time polymerase chain reaction (RT-qPCR). The clinical characteristics of GDM patients, healthy controls, and neonates were recorded. Then, the correlation analysis of Lnc-UCA1, miR-138, and Lnc-UCA1/miR-138 axis levels with clinicopathological characteristics was performed to explore the clinical value of Lnc-UCA1/miR-138 axis in GDM. Finally, the specificity and sensitivity of Lnc-UCA1, miR-138, and Lnc-UCA1/miR-138 axis for GDM diagnosis was evaluated using receiver operating characteristic (ROC) curves.

Results: Our present study found that, when compared with healthy pregnancies, the expression levels of Lnc-UCA1 and miR--138 were increased and decreased, respectively, and Lnc-UCA1/miR-138 axis profile was elevated. Second, Lnc-UCA1 and Lnc-UCA1/miR-138 axis were positively correlated with fasting glucose, one-hour glucose, and two-hour glucose, while miR-138 showed the opposite trend. Furthermore, the area under the ROC curve (AUC) were 0.8196, 0.8021, and 0.8901 for diagnostic efficiencies of Lnc-UCA1, miR-138, and Lnc-UCA1/miR-138, respectively. In addition, higher profiles of Lnc-UCA1 were correlated with birth asphyxia of neonate.

Conclusions: Circulating Lnc-UCA1/miR-138 axis might be involved in the pathogenesis of GDM and could function as a novel and effective biomarker for GDM risk and neonatal prognosis.

Keywords: LncRNA; miRNA; gestational diabetes mellitus; disease severity

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INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy, affecting approximately 3–8% of pregnant women all over the world [1, 2]. With the development of society and the improvement of living standards, the prevalence of obesity in women of childbearing age increases, and the incidence of gestational diabetes mellitus (GDM) is on the rise as well [3, 4]. GDM increases the risk of metabolic diseases in pregnant women and neonates, such as hyperbilirubinemia, gestational hypertension, preterm deliver and macrosomia [5].

Therefore, it is of great need to explore novel and rapidly measurable biomarkers for assisting on the identification of GDM and prognosis prediction of neonates. At present, due to the rapid development of science and high-throughput sequencing technology widely used, the detection accuracy and cost of non-coding RNA have been improved and greatly reduced, respectively. Therefore, non-coding RNA possess great value as a predictive marker and therapeutic target in GDM patients, among which, long noncoding RNAs (LncRNAs) and microRNAs (miRNAs) have been the most studied [6, 7], making continuous progress in the exploration pathogenesis of GDM.

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LncRNAs are novel regulators involved in many cellular processes, including cell growth, proliferation, differentiation, and apoptosis [8]. Long noncoding RNA urothelial carcinoma-associated 1 (Lnc-UCA1), locating on chromosome 14q13.12 region and encoding 3 isoforms, is found to be implicated in various diseases, especially metabolic diseases [9–12]. As a direct target of Lnc-UCA1, miR-138 is also closely related to pathogenesis of type 2 diabetes mellitus [13], diabetic nephropathy [14], and GDM [15]. However, the role of Lnc-UCA1/miR-138 axis in GDM remains unknown. Our present study, first, was determined the abundance changes of Lnc-UCA1/miR-138 axis in GDM patients. Additionally, the potential predictive value of Lnc-UCA1/miR-138 was evaluated in GDM as well.

MATERIAL AND METHODS

Subjects recruit

In this study, there was a total of 120 subjects, including 60 GDM patients and 60 normal healthy pregnant women, were recruited. From June 2020 to December 2020, the subjects were the 24 to 28 weeks pregnancy women who underwent obstetric examination at the obstetric clinic of Maternal and Child Health Hospital of Hubei Province, all the subjects were numbered and registered.

The inclusion criteria of GDM patients were as follows: (1) Meet the diagnostic standards formulated by the American Diabetes Association in 2012 [16]; (2) Based on the results of 75 g oral glucose tolerance test (OGTT) performed 24–28 weeks of gestation, at least one abnormal glucose level (fasting glucose ≥ 5.1 mmol/L, one-hour OGTT ≥ 10.0 mmol/L, or two-hour OGTT ≥ 8.5 mmol/L) after 75 g glucose administration; (3) Natural conception and single birth gestation; (4) No internal and surgical diseases before and during pregnancy, including mental disorders, malignant tumors, endocrine and metabolic diseases, and severe cardiac, liver, pulmonary, renal diseases; (5) No history of smoking or drinking; (6) Not taken any hypoglycemic medicine.

Furthermore, the GDM patients and healthy pregnant women were excluded as follows: (1) Labor because of fetal malformation; (2) Patient was lost during the delivery and could not know the outcome of the delivery.

The ethical approval (Ethical number: 2021 IEC LW020) was obtained from the Ethics Committee of Maternal and Child Health Hospital of Hubei Province, and informed written maternal consents were obtained from all subjects.

Observation indicators collection

During the 24–28 weeks of pregnancy examination, the subjects' age, weight, height, family history of diabetes, number of pregnancies, number of births, history of abortion, and other medical history were recorded in detail. The levels of high-density lipoprotein-cholesterol, low density lipoprotein-cholesterol, total cholesterol, and triglyceride were measured, respectively. After the delivery, the body weight, body length, premature delivery, and pathological jaundice of neonates were recorded as well.

Blood sample collection and RT-qPCR assay

After fasting overnight, we collected a venous blood sample from each participant at different points of time for biochemical tests. Total RNA was isolated from each blood sample using TRIzol reagent. The concentration and purity of RNA was examined by NanoDrop. A PrimeScript RT reagent kit was used to synthesize cDNA according to the manufacturer's instruction, subsequently the cDNA was kept at −80°C until use. The PCR was performed to calculate the relative expressions of UCA1 and miR-138 by SYBR green I Master Mix kit on a 7500 Real-Time PCR System.

The U6 and GAPDH were served as internal controls for miR-138 and Lnc-UCA1, respectively. The formula $2^{-\Delta\Delta Ct}$ was used to calculate the relative expression. The primers designed to amplify the LncRNA and miRNA transcripts were listed in Table 1.

Statistical analysis

The data was expressed as mean ± SD. GraphPad 7.0 (GraphPad Software, Inc., USA) were used to analyze the clinical data of this study. Student's t-test and one-way ANOVA were used to compare the differences. The correlation analysis was performed by the Pearson correlation method. $P < 0.05$ was considered statistically significant. The diagnostic value was assessed by specificity, sensitivity, and receiver operating characteristic (ROC) curve.

RESULTS

Clinical characteristics of subjects

The clinical characteristics of all subjects were listed in Table 2 in detail. There were no significant differences between healthy pregnant women and GDM patients, including age, body mass index, and hyperlipidemia status. The fasting glucose, one-hour glucose, and two-hour glucose levels were remarkably higher in the GDM patients than those of healthy controls, with a significant between-group difference ($p < 0.05$).

Table 1. Primer sequences used to detect expression of long noncoding RNA urothelial carcinoma-associated 1 (Lnc-UCA1) and miR-138

Non coding RNA	5′-3′ primer sequence	
Lnc-UCA1	Forward	5′-CCCTACCCCAGTAATCCCCA-3′
	Reverse	5′- ACGTC CTCGG TTCTTCAGAC-3′
MiR-138	Forward	5′-GCCGAGAGCTGGTGTTGTGAA-3
	Reverse	5′-CTCAACTGGTGTCGTGGA-3′

Table 2. Clinical data for the gestational diabetes mellitus (GDM) patients and healthy controls

Characteristics	Healthy controls (n = 60)	GDM cases (n = 60)	p value
Age [years]	29.83 ± 3.47	30.10 ± 2.76	> 0.05
Body mass index	20.43 ± 2.14	21.24 ± 2.91	> 0.05
Fasting glucose [mmol/L]	4.54 ± 0.51	4.84 ± 0.57	< 0.01
One hour glucose [mmol/L]	7.53 ± 1.22	9.39 ± 1.93	< 0.01
Two hour glucose [mmol/L]	6.52 ± 0.94	8.39 ± 0.95	< 0.01
Triglyceride [mmol/L]	3.67 ± 1.68	4.00 + 1.44	> 0.05
Total cholesterol[mmol/L]	6.57 ± 1.24	6.33 ± 1.17	> 0.05
High-density lipoprotein [mmol/L]	1.84 ± 0.40	1.76 ± 0.33	> 0.05
Low-density lipoprotein [mmol/L]	3.84 ± 0.94	3.63 ± 0.86	> 0.05

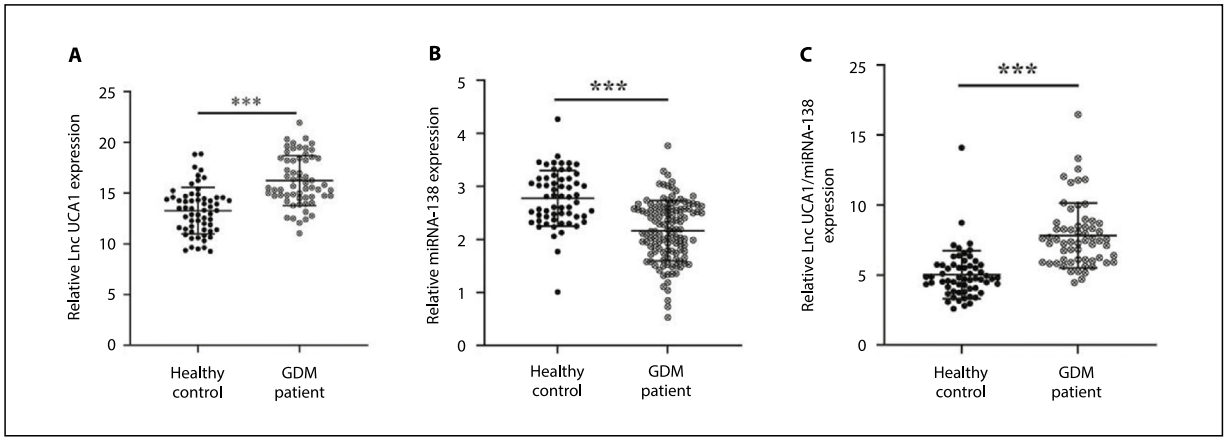

Figure 1. The relative expressions of long noncoding RNA urothelial carcinoma-associated 1 (Lnc-UCA1), miR-138 and Lnc-UCA1/miR-138 axis in the plasma of 120 samples from gestational diabetes mellitus (GDM) patients and healthy pregnant women; ***p < 0.0001

Plasma Lnc-UCA1, miRNA-138, Lnc-UCA1/ /miRNA-138 axis expression

Compared with healthy pregnancies, plasma Lnc-UCA1 was up-regulated, while plasma miR-138 was decreased in the GDM groups, respectively (Fig. 1). The Lnc-UCA1/miRNA-138 axis was increased in the GDM patients than that in healthy control. In all, the plasma profiles of Lnc-UCA1, miR-138, and Lnc-UCA1/miRNA-138 axis were abnormal in GDM patients compared with healthy controls.

Association of Lnc-UCA1, miR-138, and Lnc-UCA1/miRNA-138 axis with glucose indices

The expression of Lnc-UCA1 was positively associated with fasting glucose (r =0.1830; p = 0.0227;), one-hour glucose (r = 0.3749; p = 0.001;), and two-hour glucose (r = 0.2940; p = 0.006), while miR-138 relative expression was negatively associated with fasting glucose (r = –0.1098; p = 0.1162), one-hour glucose (r = –0.2574; p = 0.0023), and two-hour glucose (r = –0.2356; p = 0.0048) in GDM patients. Most importantly, the Lnc-UCA1/miR-138 axis was positively correlated with fasting glucose (r = 0.1197; p = 0.0965), one-hour glucose (r = 0.3824; p < 0.001), and two-hour glucose (r = 0.2647; p = 0.0017) as well (Fig. 2).

The values of Lnc-UCA1, miR-138, and Lnc-UCA1/miRNA-138-5p axis for predicting GDM risk

Logistic regression analysis showed that the relative expressions of Lnc-UCA1, miR-138, and Lnc-UCA1/miRNA--138-5p axis could well distinguish healthy and GDM (Tab. 3). We also preformed ROC curve to evaluate the significance of Lnc-UCA1, miR-138, and Lnc-UCA1/miR-138 axis in GDM. The results of ROC curves analysis indicated that Lnc-UCA1, miR-138 expressions exhibited fairly good predictive values for GDM risk with AUCs of 0.8196 (95% CI 0.7452–0.8940) and 0.8021 (95% CI 0.7244–0.8798), and Lnc-UCA1/miR-138 axis revealed numerically increased GDM risk for pregnancies with AUC 0.8901 (95% CI 0.8316–0.9487) (Fig. 3).

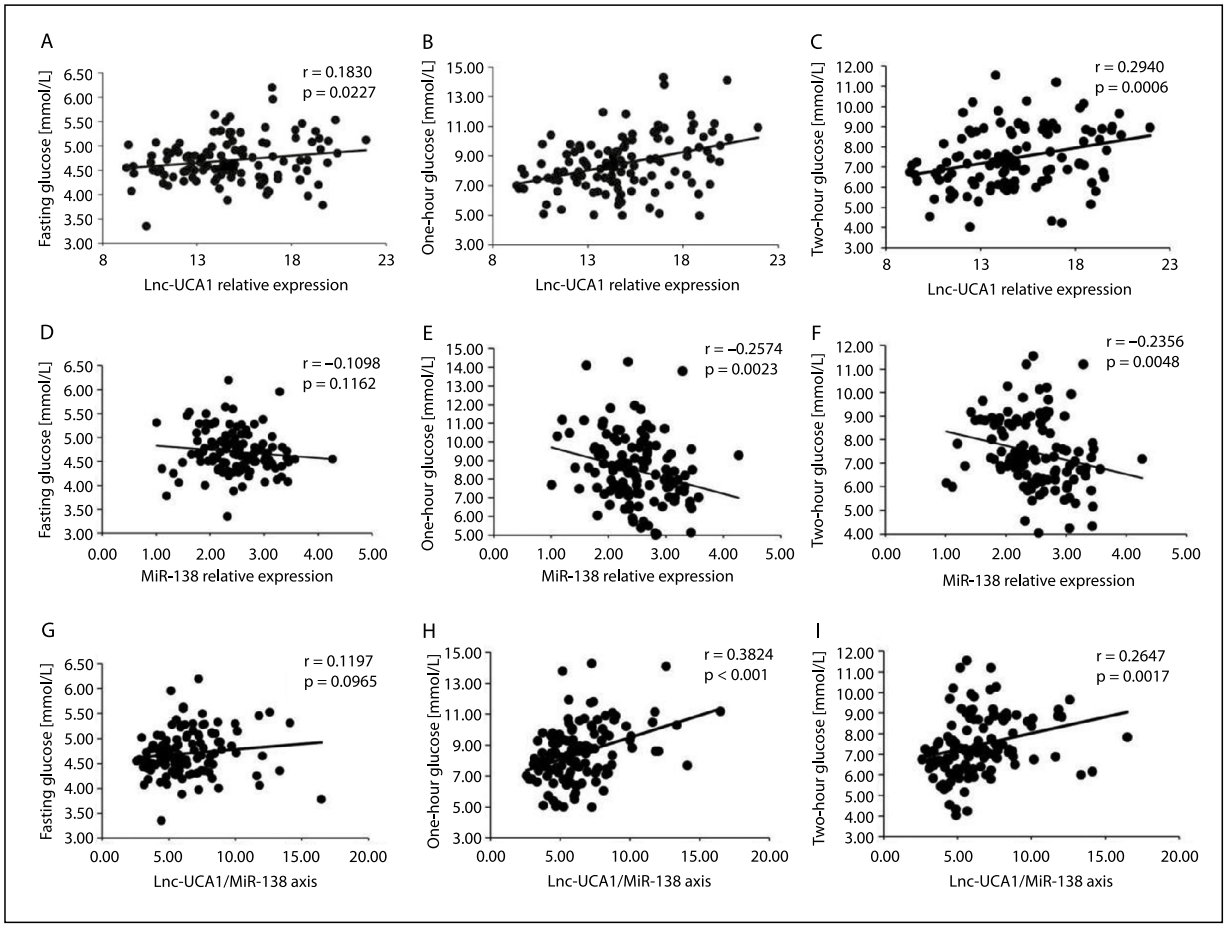

Figure 2. The correlation analysis of long noncoding RNA urothelial carcinoma-associated 1 (Lnc-UCA1, miR-138 and Lnc-UCA1/miR-138 axis and glucose indexes

Table 3. Results of logistic regression analysis

Biomarker	SE	OR	95% CI	p value
Lnc-UCA1	0.1048	5.485	0.3431 to 0.7574	< 0.001
MiR-138	0.5141	1.085	–3.608 to –1.578	< 0.001
Lnc-UCA1/miRNA-138	0.1804	13.027	0.6217 to 1.333	< 0.001

CI — confidence interval; Lnc-UCA1 — long noncoding RNA urothelial carcinoma-associated 1; miRNA — microRNA; OR — odds ratio

The cutoff value for Lnc-UCA1, miR-138, and Lnc-UCA1/miR-138 axis were, sensitivity were 14.73, 2.24 and 5.82, specificity were 75%, 93% and 87%, and accuracy were 0.78, 0.74 and 0.83, which indicating remarkable performances for Lnc-UCA1, miR-138, and Lnc-UCA1/miR-138 axis in GDM diagnosis (Tab. 4, Fig. 4).

Association of Lnc-UCA1, miR-138, and Lnc-UCA1/miRNA-138 axis neonatal prognosis

Plasma expressions of Lnc-UCA1 and miR-138 in GDM patients were associated with birth asphyxia. Regarding the birth asphyxia of neonate, Lnc-UCA1 relative expression ($X^2 = 4.36$; $p < 0.05$) was positively associated with birth asphyxia, while miR-138 relative expression was not obviously relatively correlated with birth asphyxia of neonate ($X^2 = 0.80$; $p > 0.05$) (Tab. 5).

DISCUSSION

Due to the increasing incidence of GDM worldwide, and the undiagnosed condition of GDM, medical personnel face great challenges in the management and prognosis of the disease. It is urgent to identify biomarkers to accurately monitor the pathogenesis of GDM in order to reduce

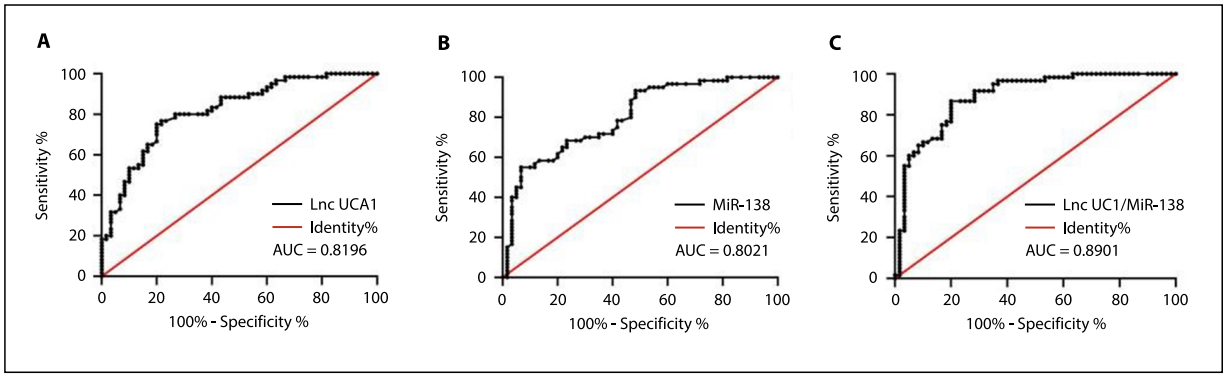

Figure 3. Long noncoding RNA urothelial carcinoma-associated 1 (Lnc-UCA1), miR-138 and Lnc-UCA1/miR-138 axis had good predictive values for gestational diabetes mellitus; AUC — receiver operating characteristic curve

Table 4. Receiver operating characteristic (ROC) parameters for gestational diabetes mellitus diagnosis using plasma long noncoding RNA urothelial carcinoma-associated 1 (Lnc-UCA1)/microRNA (miRNA)-138 expression

Biomarker	Cut off	Sensitivity	Specificity	Accuracy	AUC	p value
Lnc-UCA1	14.73	75%	80%	0.78	0.8196	< 0.0001
MiR-138	2.24	93%	55%	0.74	0.8021	< 0.0001
Lnc-UCA1/miRNA-138	5.82	87%	80%	0.83	0.8901	< 0.0001

AUC — receiver operating characteristic curve

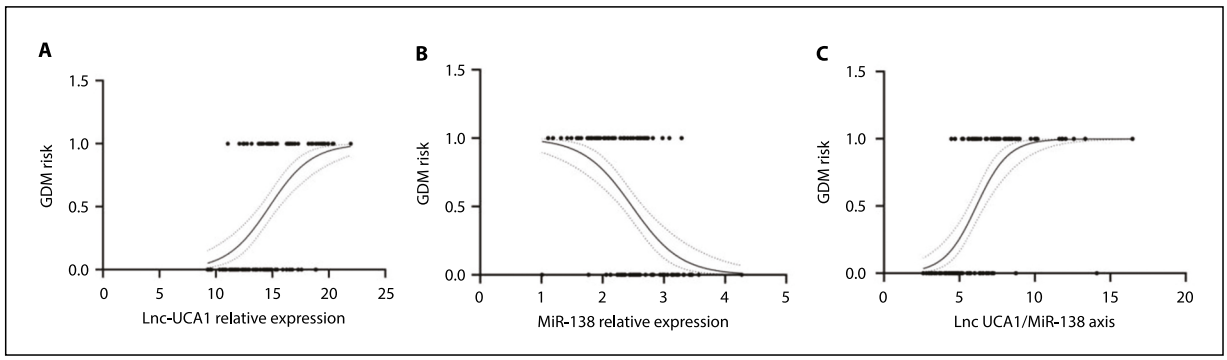

Figure 4. Logistic regression analysis between Lnc-UCA1, miR-138 and Lnc-UCA1/miR-138 axis and gestational diabetes mellitus; GDM — gestational diabetes mellitus; Lnc-UCA1 — long noncoding RNA urothelial carcinoma-associated 1

Table 5. The relationship between plasma levels of long noncoding RNA urothelial carcinoma-associated 1 (Lnc-UCA1)/microRNA (miRNA) and neonate outcomes

Category	Group	Cases	Lnc-UCA1 relative expression		X^2	p value	MiRNA relative expression		X^2	p value
			High (n = 30)	Low (n = 30)			High (n = 30)	Low (n = 30)		
Body weight	> 4.0 kg	7	5 (16.67)	2 (6.67)	0.11	> 0.05	3 (10.00)	4 (13.33)	0.00	> 0.05
	≤ 4.0 kg	53	25 (83.33)	28 (93.33)			27 (90.00)	26 (86.67)		
Birth asphyxia	Yes	15	11 (36.67)	4 (13.33)	4.36	**< 0.05**	6 (20.00)	9 (30.00)	0.80	> 0.05
	No	45	19 (63.33)	26 (86.67)			24 (80.00)	21 (70.00)		

maternal and infant morbidity and mortality risk. Circulating non-coding RNAs, considered as new 'hormones', are stably expressed in the blood and act as mediators of tissue interactions, playing a role in both physiological conditions and disease pathological process. Furthermore, non-coding RNAs play an important role in metabolism diseases, such

as pancreatic development [17], insulin secretion [18], and insulin deficiency [19]. Therefore, non-coding miRNAs are potential biomarkers for disease.

In the present study, we found that, on the hand, Lnc-UCA1, miRNA-138, and Lnc-UCA1/miRNA-138 axis showed closely association with GDM risk; on the other hand, Lnc-UCA1 and Lnc-UCA1/miRNA-138 were positively associated with, however, miR-138 was negatively associated with glucose indices, including fasting glucose, one-hour glucose, and two-hour glucose in GDM patients. Finally, higher profiles of Lnc-UCA1 and Lnc-UCA1/miRNA-138 axis, lower expression of miR-138 showed adverse effects for neonatal prognosis. Lnc-UCA1, is transcribed from human chromosome 14q13.12. As newly discovered LncRNAs, it is found that Lnc-UCA1 participates in series of diseases. Inhibition of Lnc-UCA1 level induces primary cardiomyocytes apoptosis. Lnc-UCA1 suppresses pilocarpine-induced epilepsy by inhibiting apoptosis of hippocampal neurons and improving brain injury [20, 21]. In terms of metabolic diseases, previous study indicates that induction of Lnc-UCA1 resultes in repair of hyperglycemic vascular smooth muscle cells (VSMCs). Inhibition of Lnc-UAC1 expressions remarkably reduces viability and invasive cell number in hyperglycemic VSMCs [11]. Huang et al. [22] report that the relative expression of Lnc-UCA1 elevates in diabetic retinopathy patients. Silencing of Lnc-UCA1 inhibites proliferation, angiogenesis and migration of HRECs cells under high glucose condition.

As for miR-138, the expression of miR-138 up-regulates in the insulin-resistant HepG2 cells. Knockdown of miR-138--5p enhances glucose uptake and glycogen synthesis of insulin-resistant HepG2 cells and reduces glucose concentration in medium, indicating that decrease of miR-138-5p improves insulin-resistant [23]. In addition, it is discovered that Lnc-UCA1 directly combines with miR-138 and subsequently play a variety of biological roles, affecting activities of various downstream signaling pathways [24]. Based on these previous studies that the effects of Lnc-UCA1 and miR-138 on metabolism disorders, we speculated that Lnc-UCA1, miR-138 and Lnc-UCA1/miR-138 axis might be novel biomarkers for diagnosis and treatment of metabolism disorders. However, recently, there were no study focused on the roles of these factors in the pathological process of GDM. Our present study indicated that, compared with healthy pregnancies, the relative levels of Lnc-UCA1 and Lnc-UCA1/miR-138 axis were increased in the plasma of GDM patients, while relative levels of miR-138 was reduced. The relative expressions of Lnc-UCA1, miR-138, and Lnc-UCA1/miR-138 axis were closely associated with glucose indices in GDM patients. In addition to observation of these factors' expression profiles, and interaction between expression profiles with disease indexes, the diagnostic values were evaluated as well. ROC curve analysis elucidated that Lnc-UCA1 (AUC = 0.8196; 95% CI 0.7452–0.8940), miR-138 (0.8021; 95% CI 0.7244–0.8798), and Lnc-UCA1/miR--138 axis (0.8901; 95% CI 0.8316–0.9487) were all excellent value for predicting GDM risk.

Additionally, because of fetal excessive growth, the offspring of GDM patients are more likely to be macrosomia, leading to shoulder dystocia, childbirth trauma, and preterm delivery and birth asphyxia, all of which are negative impacts of GDM [25]. Thus, we observed the neonatal indicators as well. It was disclosed that higher levels of Lnc-UCA1 ($X^2 = 4.36$; $p < 0.05$) exhibited closely associated with high risk of birth asphyxia.

LncRNA influences the post-transcriptional mechanism to regulate mRNA expression by competing with miRNAs. Therefore, LncRNAs and miRNAs can form a complex regulatory network and participate in the procedure of disease occurrence and development [17]. Recently, Zhang [26] revealed that LncRNA MEG3 is highly expressed in blood and placental villous tissues of GDM patients, knockdown of LncRNA MEG3 promotes the viability, migration and invasion of placental trophoblast cells, and reduces apoptosis. Next generation sequencing discoveris that 13 microRNAs significantly upregulate, while 14 microRNAs downregulate in GDM compared to healthy controls [27]. Based on the previous study, we investigated the association between GDM and non-coding RNA. The present study constructed a system, which integrated the clinical data of patients and Lnc-UCA1 and miR-138 expression profiles, to be a potential biomarker of GDM risk in the pregnancy trimester and neonatal prognosis.

CONCLUSIONS

There were several limitations in our study. First, the glucose indexes were acquired between 24 to 28 weeks of gestation, we did not evaluate changes in the expression profile of Lnc-UCA1 /miR-138 axis during the whole pregnancy.

Second, the sample size of this study was relatively small, which might reduce the statistical effectiveness. In addition, this study did not involve the molecular mechanism of Lnc-UCA1 /miR-138 axis regulating the progression of GDM. Therefore, our subsequent studies will include a larger sample size, longer follow-up period and more in-depth molecular mechanisms involved.

In all, the level of circulating Lnc-UCA1/miR-138 axis is abnormal in GDM patients and can function as a potential biomarker for predicting GDM risk.

Article information and declarations

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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