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Circulating miR-486-3p as a potential biomarker for the diagnosis of gestational diabetes mellitus and the prediction of adverse pregnancy outcomes

Yaqin Hu[1†], Yukai Zeng[2†], Xiaoshuang Du[3,4], Qi Li[5], Yumei Cao[4], Huihui Song[4], Zhenlan Wu[4] and Yingxuan Huang[6,7*]

Abstract

Objective Gestational diabetes mellitus (GDM) seriously endangers the health of pregnant women and their offspring. Early prediction and diagnosis allow timely treatment of GDM, preventing adverse pregnancy outcomes and related diseases. This research aims to explore the predictive significance of miR-486-3p expression levels in diagnosing GDM in early pregnancy.

Methods A retrospective study was conducted by enrolling 103 subjects with GDM and 98 healthy subjects. qRT-PCR was used to analyze the expression level of miR-486-3p. The chi-square test and t-test were used to evaluate the differences in miR-486-3p expression levels between the GDM and control groups. The predictive value of miR-486-3p in early diagnosis of GDM was analyzed by receiver operating characteristic (ROC). Potential indicators that may lead to adverse pregnancy outcomes in patients with GDM were predicted by multivariate logistic regression analysis.

Results Downregulation of miR-486-3p expression level was observed in the GDM group compared with healthy individuals. The predictive value of miR-486-3p for early diagnosis of GDM was indicated by the ROC curve. The expression level of miR-486-3p in the GDM group was negatively correlated with glycated hemoglobin (HbA1c), fasting blood glucose (FBG), homeostasis model-insulin resistance index (HOMA-IR), and leptin (LEP). Multivariate logistic regression analysis suggested that miR-486-3p, HbA1c, HOMA-IR, and FBG could be regarded as adverse pregnancy outcome risk factors in GDM subjects.

Conclusion miR-486-3p showed a clinical predictive value for GDM in early pregnancy. miR-486-3p, HbA1c, HOMA-IR, and FBG indicators can be considered adverse pregnancy outcome risk factors in GDM patients.

Keywords miR-486-3p, GDM, Biomarker, Diagnosis

†Yaqin Hu and Yukai Zeng contributed equally to this work.

*Correspondence:
Yingxuan Huang
gxhuangyx@163.com
[1]Department of Endocrinology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang 330006, China
[2]School of Biomedical Engineering, Capital Medical University, Beijing 100069, China
[3]Shandong Second Medical University, Weifang 261000, China
[4]Obstetrics and Gynecology Center, Weifang People's Hospital, Weifang 261000, China
[5]Center of Reproductive Medicine, Qingdao Women and Children's Hospital, Qingdao 266000, China
[6]Key Laboratory of Research and Development on Clinical Molecular Diagnosis for High-Incidence Diseases of Baise, Baise 533000, China
[7]Pediatric Intensive Care Unit, The Affiliated Hospital of Youjiang Medical University for Nationalities, No. 18, Zhongshan 2nd Road, Youjiang District, 533000 Baise, China

Instructions

Gestational diabetes mellitus (GDM) is defined as an abnormality of glucose metabolism in a pregnant woman who has not yet reached the explicit diagnostic criteria for diabetes and is a common complication during gestation [1–3]. In conjunction with the expansion of the global economy and the enhancement of living standards worldwide, the prevalence of GDM is on the ascendant, exerting a detrimental impact on the overall health of pregnant women and their offspring [4]. The short-term impact of GDM on pregnant women is primarily manifested in the form of adverse pregnancy outcomes such as fetal death, macrosomia, preterm birth, cesarean section, neonatal hypoglycemia, low Apgar scores, and the necessity for neonatal intensive care [5–7]. Long-term effects of GDM include an increased risk of developing diseases like diabetes mellitus, angiocardiopathy, and metabolic disease [8–10]. Additionally, there is a higher recurrence rate of GDM in subsequent pregnancies of GDM patients. The risk of obesity and diabetes in infants born to patients with GDM would also be increased during the period of growth [11]. The progression of GDM represents a significant threat to the life and health of pregnant women and their fetuses. This underscores the paramount importance of rational screening strategies for GDM.

MicroRNA (miRNA) is a non-coding single-stranded RNA molecule encoded by endogenous genes, and the length of miRNAs is about 22 nucleotides. MiRNAs play a pivotal role in gene expression post-transcription, with estimates suggesting that approximately one-third of genes of human were regulated by miRNAs [12]. The most common mechanism of action of miRNAs is binding to the 3'UTR of mRNAs and inhibiting the expression of target genes [13]. It has been established by plenty of studies that microRNAs are involved in the progression of GDM and exhibit abnormal expression levels in patients with GDM. For instance, miR-195-5p was found to be upregulated in GDM patients and could serve as a diagnostic biomarker for patients with a high risk of GDM [14]. Furthermore, miR-96-5p, miR-409-5p, and miR-21 were all observed to be dysregulated in GDM patients and involved in the GDM progression [15–17].

In an integrated analysis of miRNAs associated with GDM, miR-486-3p was identified to be dysregulated in the progression of GDM [18]. Additionally, the dysregulated miR-486-3p was also observed in obesity, diabetes, and associated complications which were the risk factors for the development of GDM [19–21]. In consideration of the aforementioned information, it can be postulated that there may be a potential correlation between miR-486-3p and GDM. Nevertheless, the relationship between miR-486-3p and GDM remains inconclusive due to the absence of clinical data. To confirm whether miR-486-3p was dysregulated in GDM, a clinical experiment was conducted, and the miR-486-3p expression levels were analyzed in GDM patients which may provide a novel insight for GDM clinical management and identify a candidate diagnostic biomarker for GDM.

Subjects and methods

Subjects

Selection of clinical subjects

A retrospective study was conducted and a power analysis was performed using G*Power 3.1 to calculate the required sample size for this study [22]. According to a priori power analysis, the total sample size was determined to be 128, assuming an effect size of 0.5, an α error probability of 0.05, and a power of 0.8. To mitigate the potential loss of subjects, a total of 201 individuals were enrolled in the study. Subsequent post hoc analysis revealed that the achieved power was 0.941. A total of 201 subjects included 103 GDM patients (GDM group) who gave birth at Weifang People's Hospital from 2020 to 2023 and 98 healthy pregnant women (Control group) who had regular physical examinations and deliveries in the same hospital during this period. The study was approved by the Ethics Review Committee of Weifang People's Hospital, and all subjects signed the informed consent after understanding the study's purpose.

Inclusion criteria of GDM: (1) patients should be over 18 years old; (2) oral glucose tolerance tests (OGTT) should be performed during the 24-28th week of gestation; (3) the blood glucose levels of GDM patients met or exceeded the following values: FBG ≥ 5.1 mmol/L, 1 h blood glucose ≥ 10.0 mmol/L, and 2 h blood glucose ≥ 8.5 mmol/L; (4) the clinical information was complete.

Exclusion criteria: (1) patients with serious complications such as heart disease, chronic nephrosis, and autoimmune disease; (2) patients with any kind of diabetes mellitus or other diseases affecting blood glucose before pregnancy; (3) patients with an abnormal placenta or umbilical cord.

Diagnostic criteria for GDM

All subjects underwent a 75 g OGTT during the 24-28th week of gestation, following the diagnostic criteria of the International Association of Diabetes in Pregnancy Study Groups (IADPSG) [23]. GDM could be distinguished if blood glucose levels in the subjects' samples met or exceeded the following values: FBG ≥ 5.1 mmol/L, 1 h blood glucose ≥ 10.0 mmol/L, and 2 h blood glucose ≥ 8.5 mmol/L.

Methods

Clinical general data collection

Detailed information, including age, body mass index (BMI), number of deliveries, weeks of gestation,

education degree, family history of hypertension, interpregnancy interval, HbA1c, HOMA-IR, and LEP of all subjects, was collected and recorded.

OGTT Performance: All subjects were required to fast for 8–14 h after FBG was analyzed. 75 g of glucose powder was dissolved in 200 mL of warm water and consumed within 5 min by the subjects. Blood samples were taken from the elbow vein at 1 and 2 h after glucose administration for blood glucose analysis. Through FBG, 1 and 2-hour OGTT data, GDM and healthy subjects could be diagnosed and differentiated.

Collection and processing of blood samples

The blood sample was collected from all subjects since the enrollment and at 24 to 28th gestational weeks, respectively. The serum from the blood sample was isolated using centrifugation at 4000 rpm for 10 min, followed by another round of centrifugation at 12,000 rpm for 15 min to remove all cell debris. FBG, fasting insulin (FINS), and HbA1c levels of all subjects were analyzed. HOMA-IR could be calculated by the equation (FBG (mmol/L) × FIN (mU/L)) ÷ 22.5.

RNA extraction and PCR

TRIzol reagent was used to extract the total RNA of blood samples collected from all subjects. NanoDrop-2000 (Thermo-Fisher, USA) was used to analyze the purity and concentration of the extracted RNA. Then the TaqMan MicroRNA reverse transcription kit was used to reverse RNA to cDNA. The quantification of miR-486-3p was analyzed on the 7300 RT-PCR system (Applied Biosystem, USA) using the SYBR kit (Invitrogen, USA). Finally, Eq. $2^{-\Delta\Delta Ct}$ was used to calculate the expression level of miR-486-3p, normalized to U6. The primer sequences were listed as follows: miR-486-3p forward: 5'-GTATGACGGGGCAGCTCAGTA-3' and miR-486-3p reverse, 5'-CAGTGCGTGTCGTGGAGT-3', U6 forward: 5'-GGAACGATACAGAGAAGATTAGC-3' and U6 reverse: 5'-TGGAACGCTTCACGAATTTGCG-3'.

Table 1 Comparation of baseline information between GDM group and control group

Index		GDM group ($n=103$)	Control group ($n=98$)	*P* -value
Age (Years)		30.53 ± 3.91	29.52 ± 4.22	0.08
BMI (kg/m^2)		24.74 ± 3.47	24.96 ± 2.61	0.62
Delivery times	0	48	47	0.96
	1 and 2	35	34	
	≥ 3	20	17	
Gestational weeks		12.41	12.61	0.71
HbAlc (%)		6.99 ± 1.60	6.23 ± 1.45	0.0005
HOMA-IR		4.81 ± 1.36	2.19 ± 0.76	<0.0001
LEP (ng/ml)		23.37 ± 5.28	17.93 ± 7.16	<0.0001
FBG (mmol/L)		5.45 ± 0.56	4.48 ± 0.42	<0.0001
1 h OGTT (mmol/L)		10.61 ± 0.84	7.84 ± 0.64	<0.0001
2 h OGTT (mmol/L)		8.65 ± 1.06	6.41 ± 0.69	<0.0001

Pregnancy outcomes information collection

The pregnancy outcomes, including newborn weight, placental weight, gender of the newborns, and the number of adverse pregnancy outcomes of subjects with GDM, were evaluated instantly after the delivery. Adverse outcomes include fetal death, fetal macrosomia, preterm birth, cesarean section, neonatal hypoglycemia, low Apgar scores, and neonates requiring admission to intensive care units [5–7].

Statistical analysis

Data analysis and diagram creation were performed using SPSS and GraphPad Prism, with all data expressed as mean value ± SD. Chi-square test, t-test, and correlation analysis were used for data analysis. The predictive value of miR-486-3p expression levels in GDM was evaluated by the ROC curve. Correlation analysis was utilized to assess the relationship between miR-486-3p expression level and GDM-related indicators. The risk factors for adverse pregnancy outcomes in subjects with GDM were evaluated by multivariate logistic regression analysis. Results were regarded as significant differences if $P<0.05$.

Results

General information

The baseline information of all subjects was collected in Table 1 and Supplementary Table 1.

According to information in Table 1 and Supplementary Table 1, no significant difference was observed in age ($P=0.08$), BMI ($P=0.62$), delivery times ($P=0.96$), gestational weeks ($P=0.71$), education degree ($P=0.17$), family history of hypertension ($P=0.86$), or interpregnancy interval ($P=0.80$) between the GDM group and healthy individuals. However, the HbA1c ($P=0.0005$), HOMA-IR ($P<0.0001$), and LEP ($P<0.0001$) levels in the GDM group were significantly increased compared with the control group.

Expression level of miR-486-3p in the GDM and control groups and ROC analysis

The miR-486-3p expression level in the GDM group was noticeably downregulated compared with the control group ($P<0.0001$, Fig. 1A). The ROC analysis was conducted based on the whole population set. The area under the curve (AUC) in the ROC curve was 0.875, cut-off of 0.945, and the 95% CI was 0.828–0.923 (Fig. 1B). Therefore, miR-486-3p demonstrated significant diagnostic and predictive value in distinguishing between GDM patients and healthy individuals, with sensitivity of 87.38%, specificity of 75.51%, positive predictive value of 78.95%, and negative predictive value of 85.06%.

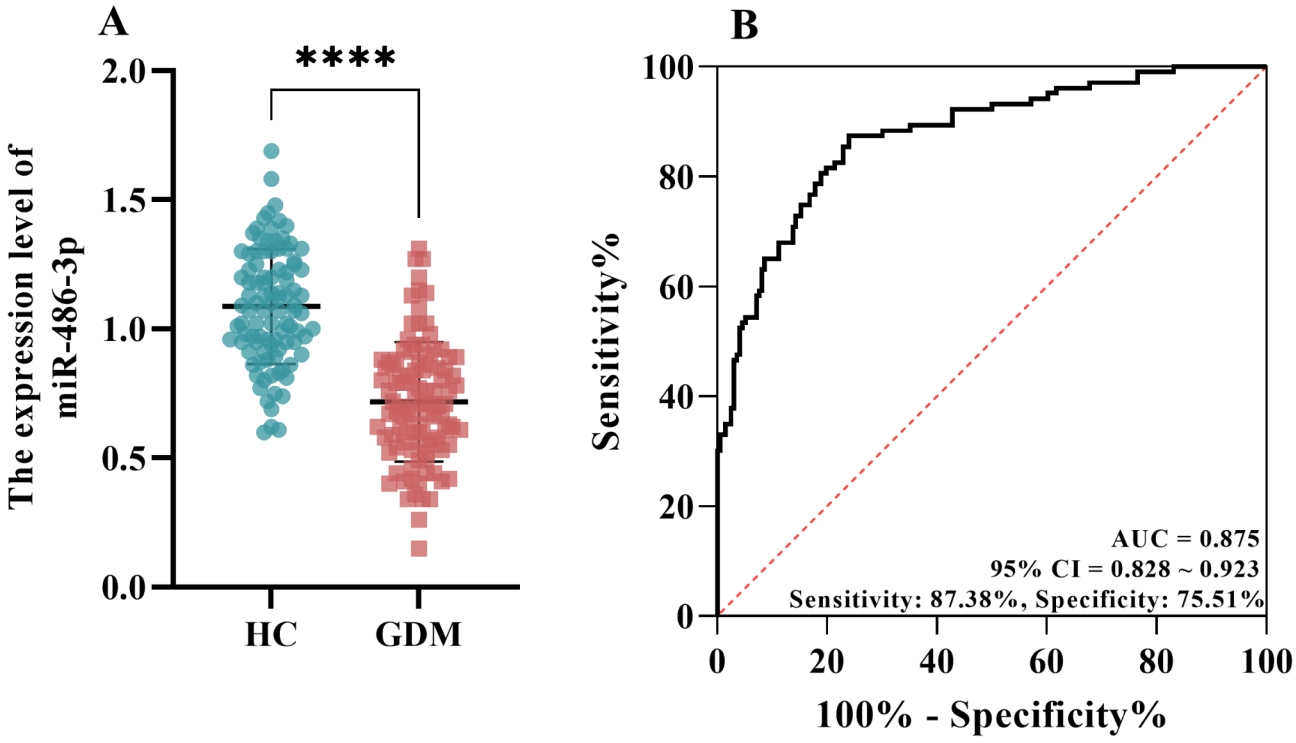

Fig. 1 MiR-486-3p expression level in subjects and its predictive value for GDM. (**A**) The miR-486-3p expression level was significantly downregulated in the GDM group compared with the control group (**** $P < 0.0001$). (**B**) The expression level of miR-486-3p demonstrated its diagnostic value in GDM

Correlation between miR-486-3p and GDM-related indicators

According to the linear regression shown in Fig. 2, the miR-486-3p expression level is significantly negatively correlated with HbA1c (r = -0.879, $P < 0.0001$, Fig. 2A), HOMA-IR (r = -0.889, $P < 0.0001$, Fig. 2B), FBG (r = -0.852, $P < 0.0001$, Fig. 2C), and LEP (r = -0.428, $P < 0.0001$, Fig. 2D), respectively, indicating a close correlation with the miR-486-3p expression level. The correlation between miR-486-3p expression level and LEP level was weaker than that with the other three indicators (HbA1c, HOMA-IR, and FBG).

Pregnancy outcomes of GDM subjects

Based on the average expression level data of miR-486-3p in the GDM group, subjects were divided into a group of high miR-486-3p expression and a group of low miR-486-3p expression. As illustrated in Fig. 3, the weight of newborns ($P < 0.01$, Fig. 3A) and placentas ($P < 0.0001$, Fig. 3B) in the low miR-486-3p group was significantly heavier than that in the high miR-486-3p group. The expression level of miR-486-3p in adverse outcomes was significantly downregulated compared to normal outcomes ($P < 0.0001$, Fig. 3C).

A significant difference was observed between the high and low miR-486-3p groups in both normal and adverse pregnancy outcomes (Table 2). There were 27 GDM subjects who developed adverse pregnancy outcomes, including 9 preterm births (7 requiring intensive care), 13 fetal macrosomia (5 with neonatal hypoglycemia), and 5 fetal intensive care. Among GDM subjects with adverse pregnancy outcomes, the number of subjects with a low miR-486-3p expression level was twice that of subjects with a high expression level. Additionally, the trend was significantly reversed in the normal pregnancy outcomes of GDM subjects ($P = 0.03$). There was no significant effect of miR-486-3p on the newborns' gender ($P = 0.86$).

Risk factor assessment for adverse outcomes in GDM subjects

Age, BMI, delivery times, gestational weeks, miR-486-3p expression level, HbA1c, HOMA-IR, LEP, and FBG were evaluated by multivariate logistic regression analysis as covariates to determine their potential as adverse pregnancy outcome risk factors in subjects with GDM. The results were shown in Table 3. The expression level of miR-486-3p ($P = 0.003$, OR: 0.164, 95% CI: 0.049–0.548) significantly predicted the adverse pregnancy outcomes of GDM subjects. Additionally, HOMA-IR ($P = 0.005$, OR: 4.954, 95% CI: 1.608–15.259), HbA1c ($P = 0.013$, OR: 4.740, 95% CI: 1.397–16.087), and FBG ($P = 0.03$, OR: 3.727, 95% CI: 1.182–11.756) could also be risk factors for the occurrence of adverse pregnancy outcomes. According to the OR values, a negative correlation between miR-486-3p expression level and the risk of adverse pregnancy outcomes in subjects with GDM was observed, while the

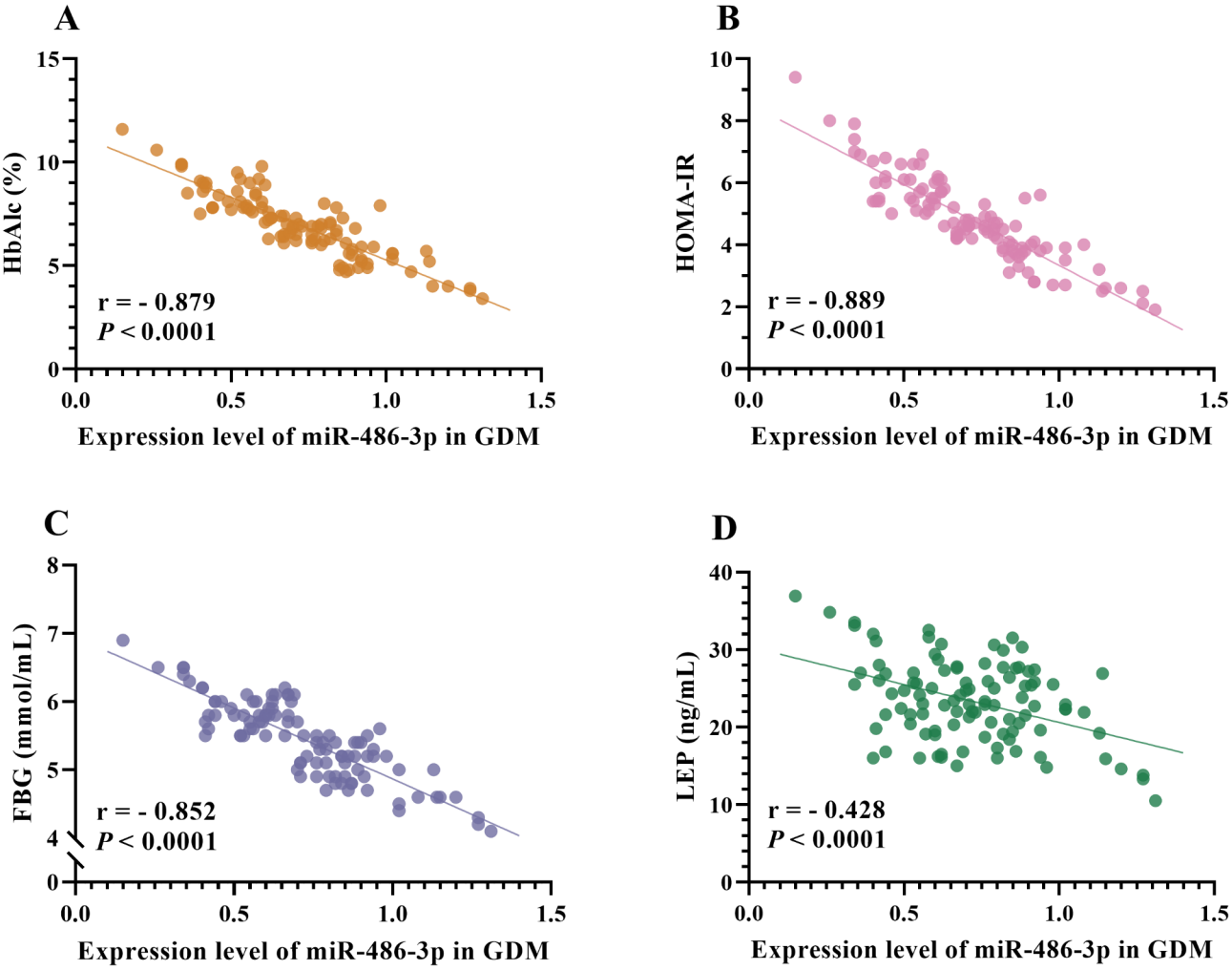

Fig. 2 Correlation between miR-486-3p and GDM-related indicators. The correlation between miR-486-3p expression level was negatively correlated with the level of HbA1c (**A**, $r = -0.8792$, **** $P < 0.0001$), HOMA-IR (**B**, $r = -0.8890$, **** $P < 0.0001$), FBG (**C**, $r = -0.8519$, **** $P < 0.0001$), and LEP (**D**, $r = -0.4275$, **** $P < 0.0001$)

levels of HOMA-IR, HbA1c, and FBG were positively correlated with the risk.

Discussion

In the last few years, GDM incidence has been rising, posing serious risks to pregnant women and their offspring [24, 25]. The pathogenesis of GDM remains unclear. However, extensive research indicates that it is a multifactorial disease linked to genetic factors, lifestyle, chronic inflammation, and adipokine [26]. Early diagnosis of GDM aids in timely intervention, preventing impacts on the health of pregnant women and decreasing the risk of adverse pregnancy outcomes. Currently, the screening of GDM primarily relies on factors such as family history, gestational age, BMI, and FBG [27]. OGTT is an effective method to screen pregnant women for GDM and is widely used in hospitals. However, OGTT is typically carried out at the 24-28th gestational week, which is relatively late for GDM diagnosis. There are studies on GDM screening through OGTT in the early gestational week, but the limit is that only high-risk GDM patients can be diagnosed, and it is not possible to screen low-risk GDM patients [28, 29]. Therefore, it is necessary to identify a predictive biomarker that allows the diagnosis and screening of GDM in early pregnancy for pregnant women.

In this study, we collected basic clinical information from all subjects. Compared with healthy subjects, the levels of HbA1c, HOMA-IR, and LEP in GDM subjects were significantly upregulated. Additionally, the expression levels of miR-486-3p in GDM patients were downregulated compared with healthy pregnant women and showed a significant negative correlation with HbA1c, HOMA-IR, and LEP. HbA1c is produced after a non-enzymatic reaction of glucose, and the average blood glucose level over the past few weeks could be effectively

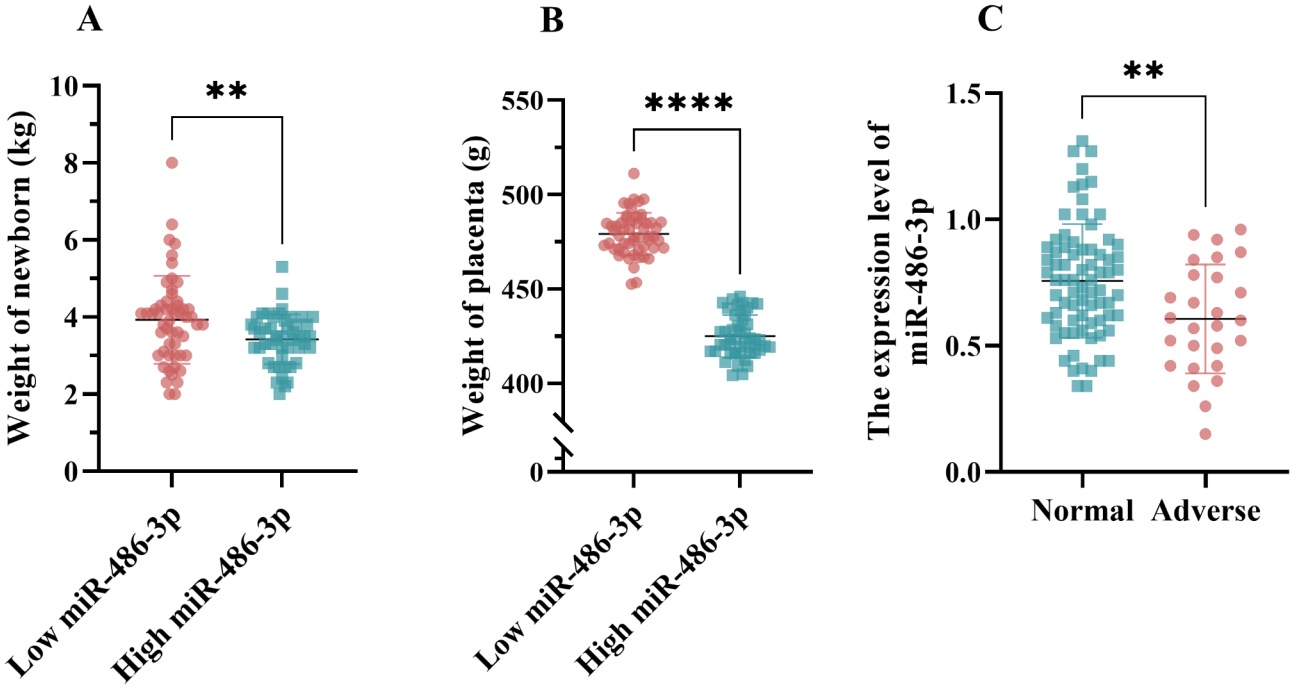

Fig. 3 Weight of newborns and placentas in GDM subjects and the expression level of miR-486-3p in GDM pregnancy outcomes. **A**, **B**) The weight of the newborns (**A**, ** $P < 0.01$) and placentas (**B**, **** $P < 0.0001$) in GDM subjects with low miR-486-3p expression levels were heavier. **C**) The expression level of miR-486-3p in adverse outcomes was downregulated compared with normal outcomes in GDM subjects, ** $P < 0.01$

Table 2 Effect of miR-486-3p expression level on pregnancy outcomes in GDM subjects

Pregnancy outcomes in GDM group		Expression level of miR-486-3p		*P* value
		Low expression	High expression	
Adverse outcome		19	8	0.03
Normal outcome		35	41	
Gender of newborn	Male	23	20	0.86
	Female	31	29	

Table 3 Multivariate logistic regression analysis of risk factors for adverse pregnancy outcomes in GDM subjects

Factor	*P*-Value	OR	95% CI
Age	0.21	2.072	0.661 ~ 6.490
BMI	0.95	1.038	0.357 ~ 3.021
Delivery time	0.99	1.008	0.334 ~ 3.044
Gestatinal week	0.40	1.603	0.532 ~ 4.832
miR-486-3p	0.003	0.164	0.049 ~ 0.548
HbAlc	0.013	4.740	1.397 ~ 16.087
HOMA-IR	0.005	4.954	1.608 ~ 15.259
LEP	0.12	2.346	0.803 ~ 6.851
FBG	0.03	3.727	1.182 ~ 11.756

reflected by HbA1c. A previous study reported that HbA1c is closely correlated with GDM, and the risk of GDM increases as the level of HbA1c rises [30]. HOMA-IR is an indicator used to evaluate insulin resistance levels in individuals and tends to increase in pregnant women with GDM during the 24–28th week of pregnancy [31, 32]. LEP, a hormone secreted by adipose tissue, is a key regulator of glucose metabolism. High LEP levels are also closely related to GDM [33]. Numerous studies have demonstrated the close correlation between HbA1c, HOMA-IR, LEP, and GDM [34–36], and these three indicators can be considered risk factors for the occurrence of adverse pregnancy outcomes in GDM patients [37–39]. This study verified the correlation between HbA1c, HOMA-IR, LEP, and GDM, and also confirmed that HbA1c, HOMA-IR, and FBG served as the risk factors for adverse pregnancy outcomes in GDM patients. For each unit increase in HbA1c, HOMA-IR, and FBG, the risk of GDM increased by 4.740, 4.954, and 3.727 times, respectively, and the results were statistically significant. The miR-486-3p expression level showed a significant negative correlation with HbA1c, HOMA-IR, and LEP, reflecting the clinical significance of miR-486-3p in GDM and adverse pregnancy outcomes. The significant diagnostic value of the expression of miR-486-3p in GDM for pregnant women in early gestational weeks was further confirmed by the ROC curve, with an ability to identify GDM patients of 87.38% and an ability to exclude the non-GDM patients of 75.51% in clinical application. Because miR-486-3p expression levels were analyzed based on blood samples collected at the time of subjects enrollment, compared with the time of OGTT performance, miR-486-3p could diagnose GDM earlier because the earliest gestational weeks of GDM subjects

enrollment was 5 weeks, and the latest gestational weeks was 20 weeks, both of which were earlier than OGTT performance, indicating the diagnostic value of miR-486-3p in early pregnancy. MiR-486-3p could also be regarded as a risk factor for adverse outcomes in GDM subjects, For each unit increase in miR-486-3p, the risk of GDM increased by 0.164 times, and the true effect size had a 95% probability of falling between 0.049 and 0.548, which was statistically significant and of clinical reference significance.

However, there were also some limitations in this study, such as the relatively small sample size and the fact that only pregnant women admitted to our hospital in the past three years were enrolled, while it is unclear if miR-486-3p expression level in GDM patients from other regions shows the same trend in early pregnancy and this might limit the applicability of the results to other populations. Furthermore, the mechanism and cause of miR-486-3p downregulation in GDM patients are still unknown. TLR4 has been identified as a downstream target of miR-486-3p [21] and it has been suggested that it plays a role in the development of GDM [40]. One potential mechanism involves the involvement of miR-486-3p in the progression of GDM through the regulation of TLR4 expression. However, further research is necessary to fully substantiate this hypothesis. A previous study reported a change in miRNA expression levels in circulating extracellular vesicles throughout the pregnancy cycle, with the number of expressed miRNAs decreasing in both healthy pregnant women and GDM patients [41]. Therefore, further studies should involve more subjects to increase the reliability of the results, and in-depth studies should be conducted on the reasons why the expression level of miR-486-3p in GDM patients was downregulated in early gestational weeks and how the expression level of miR-486-3p changes along with the pregnancy cycle. Additionally, the regulatory mechanism of miR-486-3p in GDM progression should also be investigated by the in vitro experiments.

Conclusion

In conclusion, our study demonstrated that the circulating miR-486-3p expression level in GDM patients was significantly downregulated compared with healthy individuals, and miR-486-3p could be potentially considered as a biomarker for GDM diagnosis in early pregnancy. The miR-486-3p expression level could also serve as a risk factor for evaluating adverse pregnancy outcomes in pregnant women with GDM. For further research, more participant involvement is necessary and a stronger theoretical basis for the mechanism of how circulating miR-486-3p affects pregnant women with GDM in early pregnancy needs to be provided.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07405-6.

Supplementary Material 1

Author contributions

X.S. D, and Z.L. W designed the research study. Y.Q. H, Y.K. Z, Q. L, Y.M. C, H.H. S and Y.X. H performed the research. X.S. D, Q. L, Y.M. C, H.H. S and Z.L. W analyzed the data. X.S. D, and Z.L. W wrote the manuscript. Y.Q. H, Y.K. Z and Y.X. H contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Data availability

Corresponding authors may provide data and materials.

Declarations

Ethics approval and consent to participate

The study protocol was approved by The Ethics Committee of Weifang People's Hospital and followed the principles outlined in the Declaration of Helsinki. In addition, informed consent has been obtained from the participants involved.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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