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Association of placental PPARα/γ and miR-27b expression with macrosomia in healthy pregnancy

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BACKGROUND: Peroxisomal proliferator-activated receptors (PPARs) and microRNAs (miRNAs) play important roles in the development of fetuses, whereas expression changes of PPARs and three miRNAs (miR-17, miR-27b and miR-34a) and whether these miRNAs regulate PPARs in non-GDM macrosomia placenta is unclear.
METHODS: A case–control study was performed to collect information and placental tissues on mothers and newborns of non-GDM macrosomia and normal-birth-weight infants. In vitro HTR8-SVneo cellular model was used to detect the effects of miRNAs on PPARs expression. Quantitative real-time PCR (qRT-PCR) and western blot was applied to examine the expression levels of *PPARs*, miR-17, miR-27b, and miR-34a in placental tissues and cells.
RESULTS: The PPARα/γ mRNA and protein levels were significantly up-regulated and miR-27b was down-regulated in the placenta of macrosomia group compared with in the control group, while no difference was observed in PPARβ, miR-17, and miR-34a. After adjusting for confounding factors, low miR-27b and high *PPARα/γ* mRNA expression still increased the risk of macrosomia. The PPARα/γ protein levels presented a corresponding decrease or increase when cells were transfected with miR-27b mimic or inhibitor.
CONCLUSIONS: Placental PPARα/γ and miR-27b expression were associated with non-GDM macrosomia and miR-27b probably promotes the occurrence of non-GDM macrosomia by regulating PPARα/γ protein.

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IMPACT:

- Low miR-27b and high *PPARα/γ* mRNA expression in the placenta were associated with higher risk of macrosomia.
- In vitro HTR8-SVneo cell experiment supported that miR-27b could negatively regulate the expression of PPARα and PPARγ protein.
- MiR-27b was probably involved in non-GDM macrosomia through negative regulation of PPARα/γ protein.

INTRODUCTION

Macrosomia is defined as infant's birth weight ≥ 4000 g in Asia.[1] In China, the incidence of macrosomia increased from 6.90% in 2007–2008[2] to 7.80% in 2016–2017.[3] Macrosomia, one of the common perinatal pregnancy complication, not only increases the incidence of cesarean section and postpartum hemorrhage but also contributes to adverse birth outcomes, such as fetal shoulder dystocia and brachial plexus injury,[4,5] and leads to childhood and adult overweight or obesity.[6] Gestational diabetes mellitus (GDM) has been currently known to be an independent risk factor for macrosomic neonates. With screening for gestational diabetes and glycemic control during pregnancy, the proportion of pregnant women with GDM was declining, whereas the ratio of pregnant women without gestational diabetes mellitus (non-GDM) delivering macrosomia was increasing in China and accounted for about 93% in total surviving macrosomia.[7] However, the causes and mechanism for the occurrence of non-GDM macrosomia were not entirely clear.

Peroxisome proliferator-activated receptor (PPARs) superfamily, a nuclear transcription factor, has three isoforms (PPARα, PPARβ/δ, and PPARγ). PPARs are expressed in varied tissues and play an important role in promoting fatty acid uptake, transport, and oxidation and participating in energy metabolism and balance.[8,9] Studies have reported that the mRNA expression level of *PPARγ* in placenta of low-birth-weight infants was lower than those of normal-weight infants.[10] The expression of placental PPARγ protein in large for gestational age (LGA) was higher than those of small for gestational age (SGA) and the PPARγ expression increased with higher birth weight.[11] Furthermore, our previous study also found that the expression levels of placental PPARα/γ and its downstream genes such as fatty acid translocase (FAT/CD36) and plasma membrane fatty acid-binding protein (FABPpm) in non-GDM macrosomia were significantly higher than that in the control group.[12–14] The above accumulating evidence implied that there was a link between PPARs and birth weight, whereas the

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specific mechanism of PPARs in the development of non-GDM macrosomia needs further exploration.

MicroRNAs (miRNAs) are small single-stranded non-coding RNAs that inhibit the target gene expression through mRNA degradation or translational repression, being involved in placental development, cell proliferation, and differentiation.[15] It has been reported that miR-17, miR-27b, and miR-34a could regulate lipid metabolism in different tissues and cells by targeting PPARs,[16–18] and these three miRNAs levels in pregnant women's serum delivering macrosomia were lower than in the control group.[19,20] In addition, the placental miR-17 expression level in macrosomia was not different from control group.[19] However, the expression of the other two miRNAs in macrosomia placenta has not been reported, and whether miRNAs can regulate PPARα/β/γ in non-GDM macrosomia placenta is also unknown.

Therefore, we performed the case–control study and in vitro cell experiments to test the expression changes of PPARα/β/γ and miRNAs in placental tissues and their associations with non-GDM macrosomia, aiming to provide new clues for the causes and mechanism of non-GDM macrosomia.

MATERIALS AND METHODS

Study population

A total of 72 pregnant women were recruited to this case–control study. We continuously collected the information about newborns and their mothers who underwent routine prenatal examination and delivered in the Department of Obstetrics and Gynecology of the Second Affiliated Hospital of Wenzhou Medical University from May 2018 to April 2019. The case group (macrosomia group) consisted of 36 newborns with birth weight ≥4000 g and their mothers, and the control group (normal-birth-weight group) was randomly selected 36 newborns with birth weight ranging from 2500 to 3999 g, born within 3 days before or after the birth of macrosomia, and their mothers. The neonates were included if they had no congenital malformation; or if their mother had normal pregnancy, was singleton, term delivery (gestation age ≥37 weeks), normal glucose tolerance test, and had not any of the following pregnancy complications: hypertension, hepatitis, heart disease, psychological disorders, or impaired glucose tolerance. All subjects signed informed consent and the project was approved by the ethics Committee of Wenzhou Medical University.

Data collection and placenta sample collection

The self-designed questionnaire and the hospital information collection system were used to collect the maternal demographic characteristics, pregnancy and delivery information, and newborn essential information, such as infant sex and birth weight. At the same time, after delivery of the placenta, the placenta tissue was cut to the size of 1 cm^3 from the placental chorionic layer avoiding infarcted areas, washed twice with saline solution (0.9% NaCl), and immediately placed in enzyme-free cryopreservation tube immersed with RNAlater solution (Ambion, Austin, TX). Then the sample was transported to the laboratory by dry ice, stored overnight at 4 °C, and then transferred to −80 °C for long-term storage.

Cell culture and transfection

The human placental trophoblastic cell line HTR8-SVneo (Zhongqiao Xinzhou, Shanghai, China) was cultured in DMEM-F12 medium containing 10% fetal bovine serum (Gibco, ThermoFisher, Waltham, MA) and 1% dual antibiotic (100 U/ml penicillin and 100 U/ml streptomycin (Gibco, ThermoFisher, Waltham, MA) in a 5% CO_2 cell incubator at 37 °C. When the cells were in logarithmic growth phase, they were transfected with miR-27b mimic, mimic control, inhibitor, and inhibitor control (GenePharma, Shanghai, China) using transfection reagent Lipofectamine 2000 (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions (2.5 μl Lipofectamine 2000 reagent per 6-well plate). Then the cells were cultured for 48 h for subsequent testing.

RNA extraction and quantitative real-time PCR (qRT-PCR)

Total RNA containing miRNAs was extracted from placenta tissues and cultured cells by TRIzol reagent (Invitrogen, Carlsbad, CA) and then reverse-transcribed into cDNA by reverse transcription kit (Takara, Tokyo, Japan).

Table 1. Primer sequences used for qRT-PCR.

Gene	Primer sequence (5′ → 3′)	Product size (bp)
PPARα forward	CTATCATTTGCTGTGGAGATCG	121
PPARα reverse	AAGATATCGTCCGGGTGGTT	
PPARβ forward	TCAGAAGAAGAACCGCAAC	207
PPARβ reverse	TAGGCATTGTAGATGTGCTTGG	
PPARγ forward	TACTGTCGGTTTCAGAAATGCC	141
PPARγ reverse	GTCAGCGGACTCTGGATTCAG	
GAPDH forward	CATGAGAAGTATGACAACAGCCT	113
GAPDH reverse	AGTCCTTCCACGATACCAAAGT	

Reverse transcription of miRNAs was performed using stem loop primers (Ribobio, Guangzhou, China). The primers used for qRT-PCR were synthesized by Huada (Shanghai, China), and the primer sequences for qRT-PCR are shown in Table 1. Target genes were quantified with SYBR green dye (Roche, Basle, Switzerland) and a CFX96 Touch real-time PCR detection system (Bio-Rad, Hercules, CA) according to the manufacturer's protocols. The qRT-PCR reaction conditions were 95 °C for 10 min, followed by 40 cycles of 95 °C for 10 s, 60 °C for 15 s, and 72 °C for 20 s. Finally, the temperature was elevated from 65 to 99 °C in 0.1 °C/s increments to obtain a melting curve for confirming amplification specificity. The *GAPDH* and U6 were used as the internal reference gene for *PPARs* and miRNAs, respectively. All the reactions were run in triplicate and $2^{-\Delta\Delta Ct}$ was used to calculate the relative expression of target genes.

Protein extraction and western blot analysis

All placenta tissues (20 mg) and the cultured cells were washed twice with phosphate-buffered saline (PBS), homogenized in RIPA lysis buffer (Beyotime, Shanghai, China), and centrifuged at 12,000 rpm for 5 min to get the supernatants. The total protein concentrations were detected by the Enhanced BCA Protein Assay Kit (Beyotime, Shanghai, China), and the protein was denatured after the concentration was adjusted to be consistent. Equal amounts of total protein were separated by 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis and subsequently transferred to polyvinylidene difluoride membranes (Bio-Rad, Hercules, CA). After blocking with 5% defatted milk in Tris-buffered saline with Tween 20 (TBST) for 1 h at room temperature, the membranes were then incubated overnight at 4 °C with antibodies for GAPDH, PPARα, and PPARγ (Abcam, Cambridge, UK). After TBST washing three times, the membranes were incubated for 1 h at room temperature with secondary antibody (Abcam, Cambridge, UK). The membranes were washed again and detected with enhanced chemiluminescence reagents (Biological Industry, Israel). The images were captured using the Quantity One software (Bio-Rad, Hercules, CA).

Statistical analysis

The questionnaire data were double-entered into EpiData 3.1. The data were analyzed with SPSS 14.0 (SPSS Inc., Chicago, IL) and presented with GraphPad Prism 7.0 (GraphPad Software Inc., San Diego, CA). Exploratory data analysis and Shapiro–Wilk tests were performed to determine the normality of the data distribution. Normally distributed data were expressed as means with SDs and the Student's *t* test was used to compare between-group differences, while non-normally distributed data were presented with median (P_{25}, P_{75}) and the Mann–Whitney *U* test was used. The characteristics of the participant were analyzed using the chi-square test (χ^2) or the Fisher's exact test for categorical variables. Non-conditional logistics regression analysis was used to evaluate the risk factors of macrosomia by odds ratio (OR) and 95% confidence interval (CI). Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Subject characteristics

The baseline characteristics of the study population were summarized in Table 2. A total of 36 macrosomia and 36 normal-birth-weight infants were collected in this study. The birth weight was 4215 (4125, 4333.75) g in the macrosomia group and 3390 (3260, 3550) g in the control group. There were statistical differences between two groups in gestational weight gain, gestational age, and infant sex ($P < 0.05$), while no statistical significance was observed

Table 2. Baseline characteristics of the study population.

characteristic	Control ($n = 36$)	Macrosomia ($n = 36$)	$Z/t/\chi^2$	P
Maternal age (years)	27.50 (23.75, 29.75)	30.00 (26.00,33.00)	−1.917	0.055
Pre-pregnancy BMI (kg/m²)	20.66 ± 2.31	21.69 ± 3.21	−1.547	0.126
Gestational weight gain (kg)	14.18 ± 3.78	16.53 ± 4.99	−2.237	0.028*
Gestational age (weeks)	39.50 (38.00, 40.00)	40.00 (39.00, 40.75)	−2.164	0.030*
Male fetus, *n* (%)	17 (47.2)	29 (80.6)	8.699	0.003**
History of macrosomia, *n* (%)	0 (0)	3 (8.3)	1.391	0.238
Nulliparous, *n* (%)	23 (63.9)	19 (52.8)	0.914	0.339

The statistic value Z/t was obtained from the Mann–Whitney U test and Student's t test for continuous variables in or not in normal distribution and the χ^2 (chi-square) for categorical variables.
BMI body mass index.
*$P < 0.05$; **$P < 0.01$.

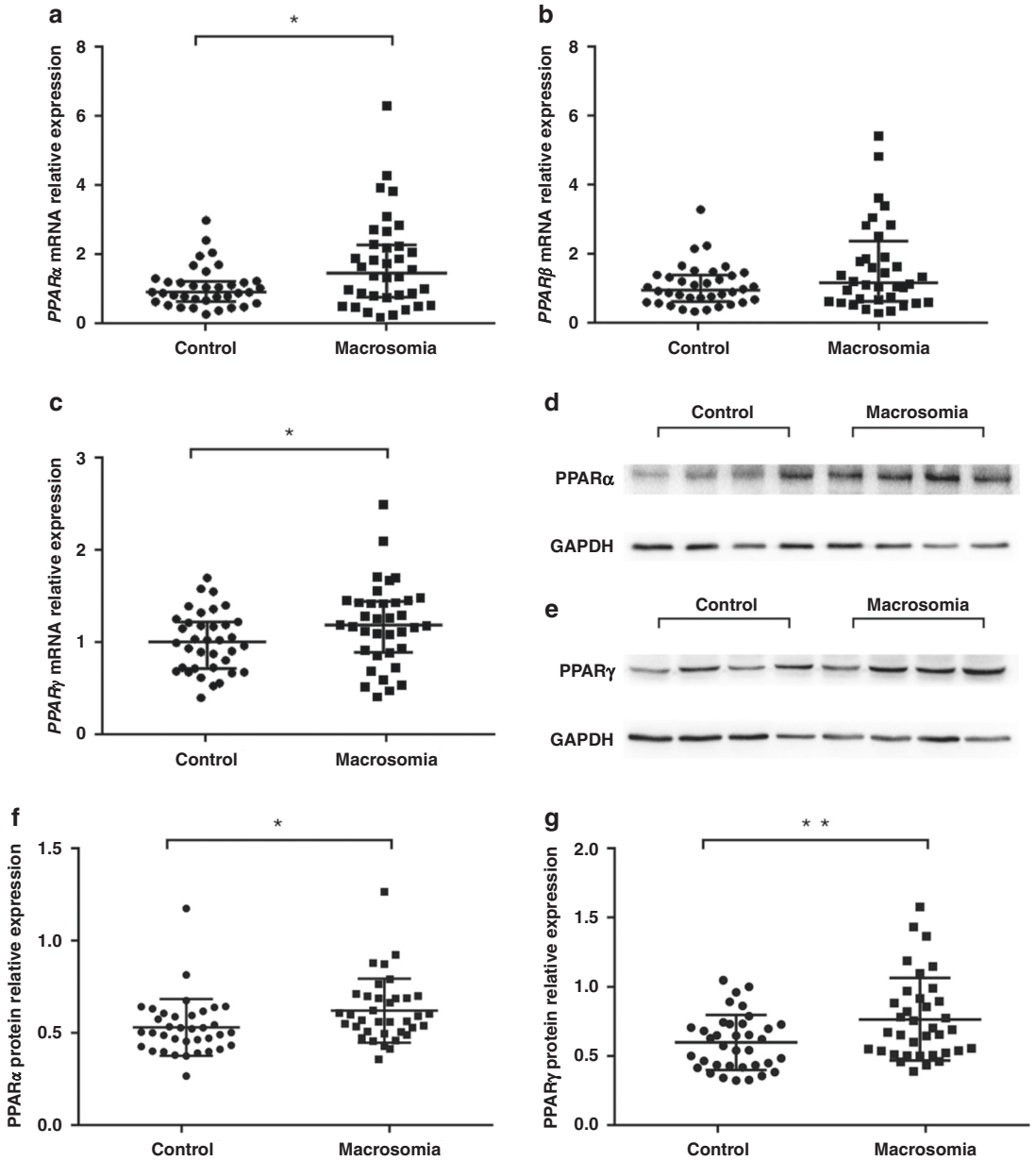

Fig. 1 The mRNA and protein expression of PPARs in placental tissues. a–c The placental *PPARα*, *PPARβ*, and *PPARγ* mRNA expression levels between macrosomia and control groups, respectively ($n = 36$ pairs). **d–e** The qualitative plots of placental PPARα and PPARγ protein expression ($n = 36$ pairs). **f–g** The quantitative graphs of placental PPARα and PPARγ protein ($n = 36$ pairs). *$P < 0.05$, **$P < 0.01$.

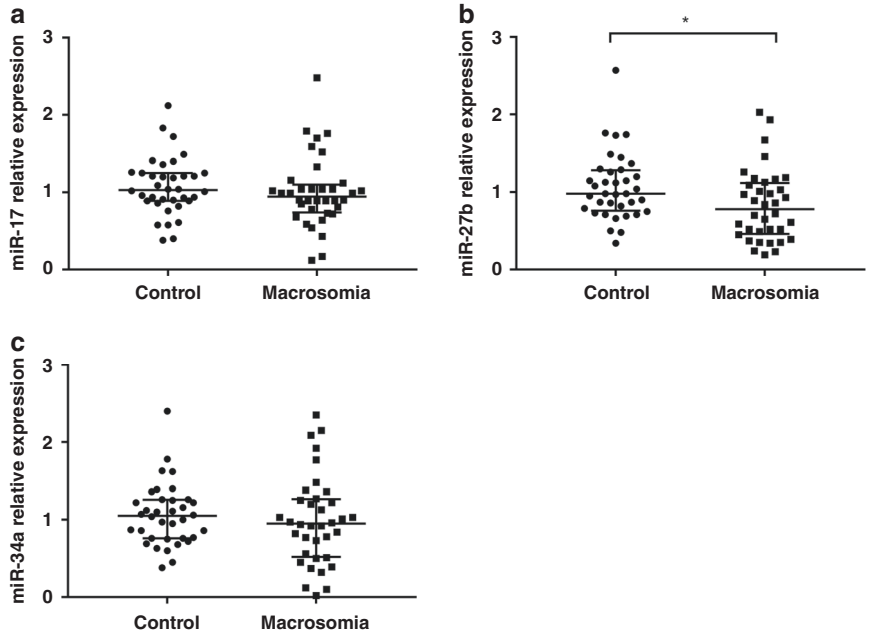

Fig. 2 The expression levels of three miRNAs in placental tissues. a–c The expression of miR-17, miR-27b, and miR-34a in the placental tissues of macrosomia and control groups ($n = 36$ pairs). *$P < 0.05$.

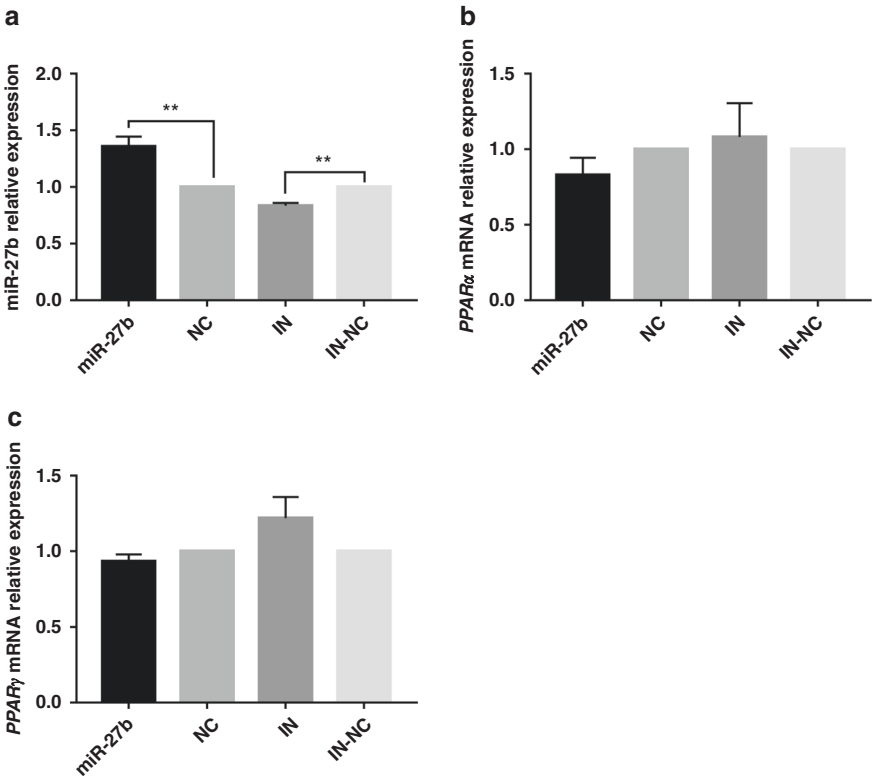

Fig. 3 The expression of miR-27b and *PPARα/γ* mRNA in HTR8-Svneo cells transfected with miR-27b. a–c The expression of miR-27b and *PPARα/γ* mRNA in cells treated with miR-27b mimic, inhibitor, and their corresponding control ($n = 4$). MiR-27b was the miR-27b mimic; NC was the miR-27b mimic control; IN was the miR-27b inhibitor; IN-NC was the miR-27b inhibitor control. **$P < 0.01$.

between two groups in other factors, including pre-pregnancy body mass index (BMI), history of macrosomia, and nulliparous.

The mRNA and protein expression levels of PPARs in placenta

To examine the placental PPARs expression, the qRT-PCR and western blot were performed. The mRNA expression levels of *PPARα* ($Z = -2.061$, $P = 0.039$) and *PPARγ* ($t = -2.077$, $P = 0.041$) in the placenta of macrosomia group were higher than those of the control group, while *PPARβ* mRNA ($Z = -1.509$, $P = 0.131$) presented an increasing trend without statistical significance (Fig. 1a–c). Meanwhile, the PPARα ($t = -2.348$, $P = 0.022$) and PPARγ ($t = -2.780$, $P = 0.007$) protein expression levels

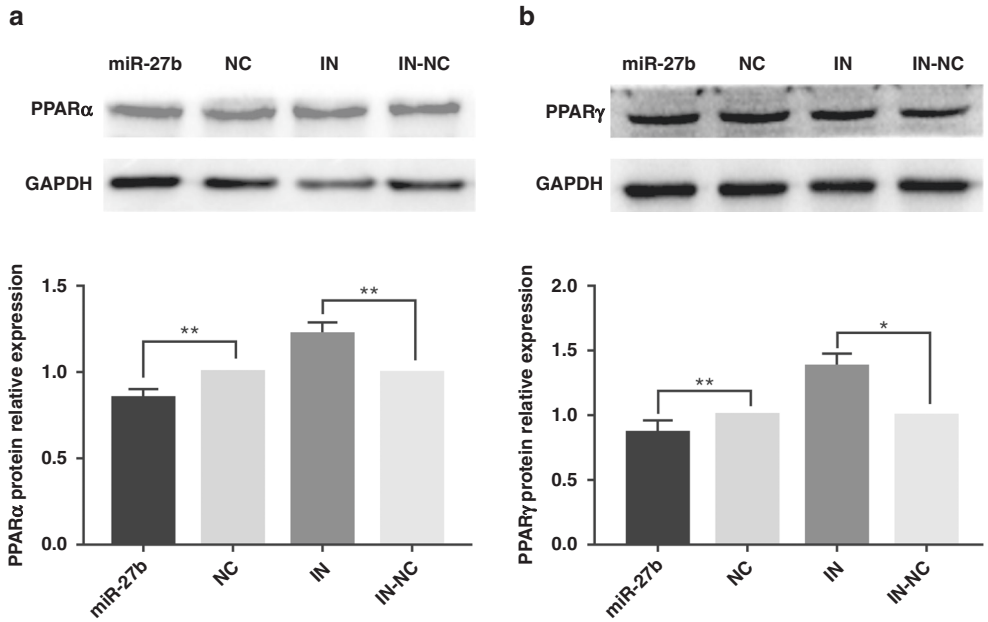

Fig. 4 The expression of PPARα/γ protein in HTR8-Svneo cells transfected with miR-27b. a, **b** The qualitative and quantitative plots of PPARα/γ protein expression levels in HTR8-Svneo cells transfected with miR-27b mimic, inhibitor, and their corresponding control ($n = 5$). MiR-27b was the miR-27b mimic; NC was the miR-27b mimic control; IN was the miR-27b inhibitor; IN-NC was the miR-27b inhibitor control. *$P <$ 0.05, **$P < 0.01$.

corresponding to the mRNA levels were meaningfully up-regulated in the macrosomia group (Fig. 1d–g), indicating that PPARα/γ might have essential effect in the development of macrosomia.

Expression levels of miR-17, miR-27b, and miR-34a in the placenta

To determine whether the miRNAs (miR-17, miR-27b, and miR-34a) participate in the development of non-GDM macrosomia, we evaluated the expression levels of the three miRNAs in placenta tissues. The miR-27b expression ($t = 2.246$, $P = 0.028$) in the placenta of macrosomia group was significantly lower than that of the control group but not found in miR-17 ($Z = -1.273$, $P = 0.203$) and miR-34a ($t = 0.592$, $P = 0.556$) (Fig. 2). Thus, we further analyzed whether miR-27b could regulate PPARα/γ expression in in vitro cell experiment.

The effects of miR-27b on PPARα/γ in HTR8-SVneo cells

To investigate whether placental miR-27b can up-regulate PPARα/γ, we transfected miR-27b mimic or inhibitor to HTR8-SVneo cells. After transfected with miR-27b mimic, the expression level of miR-27b was significantly higher than negative control ($t = 3.961$, $P = 0.007$), and in contrast, miR-27b inhibition markedly reduced the miR-27b expression ($t = -15.830$, $P = 0.001$), indicating that the cell transfection model was successfully constructed (Fig. 3a). However, neither overexpression nor inhibition of miR-27b affected the *PPARα* and *PPARγ* mRNA (Fig. 3b, c). On the contrary, the PPARα ($t = -8.239$, $P <$ 0.001) and PPARγ ($t = -4.764$, $P = 0.009$) protein levels were significantly decreased by the overexpression of miR-27b (Fig. 4a). And the miR-27b inhibition significantly caused down-regulation in PPARα ($t = 7.218$, $P < 0.001$) and PPARγ ($t = 6.193$, $P = 0.002$) protein (Fig. 4b), suggesting that miR-27b inhibited the PPAR translational protein expression rather than degrading mRNA expression.

Multivariate analysis of factors affecting macrosomia

The above evidence and literature indicated that miR-27 could exert biological process through regulating PPARα/γ,[18,21] thus PPARα and PPARγ were intermediate variables of miR-27b affecting macrosomia. Additionally, PPARα and PPARγ belonged to different subtypes of the same nuclear receptor, therefore we conducted three logistic regression models to examine factors affecting macrosomia. As shown in Table 3, after controlling factors containing infant sex, gestational age, and gestational weight gain, low miR-27b and high *PPARα* and *PPARγ* mRNA expression in the placenta could increase the risk of macrosomia.

DISCUSSION

In this study, we observed that, compared with the control group, the mRNA and protein expression levels of placental PPARα and PPARγ were significantly increased and the miR-27b levels were decreased in the macrosomia group. Furthermore, in vitro cell experiments supported that miR-27b could negatively regulate the expression of PPARα and PPARγ protein, indicating that miR-27b was likely to influence non-GDM macrosomia through PPARα/γ. After adjusting for potential confounding factors such as infant sex, gestational age, and gestational weight gain, low miR-27b as well as high *PPARα* and *PPARγ* mRNA expression increased the risk of fetal macrosomia.

PPARs belonging to the ligand-activated nuclear hormone receptor family are activated by fatty acids and critical for placental development and function, including fatty acids uptake.[22] Previous studies have demonstrated that placental PPARγ mRNA or protein expression was positively related to birth weight.[10,11] In addition, Fu et al.[23] performed immunohistochemical analysis of placenta and found that placental PPARγ-positive nuclei was less in SGA than in appropriate for gestational age (AGA). Our study was consistent with these results, and what is more, our previous research found that expression levels of the placental FAT/CD36 and FABPpm on the downstream of PPARs in non-GDM macrosomia were significantly higher than that in the normal-birth-weight group,[12,13] indicating that PPARs possibly promote the occurrence of macrosomia by affecting placenta lipid transport.

MiRNAs have been recognized as a major regulator of gene expression with regard to varied biological processes. It has been reported that miR-17, miR-27b, and miR-34a could target PPARα/β/γ gene to influence lipid metabolism in different tissues and cells.[16,17] MiR-17 reported by Li et al.[19] showed no difference in the placenta between the macrosomia group and control group, whereas the miR-17 expression in the maternal serum of the

Table 3. Multivariate logistic regression analysis of influence factors of macrosomia.

Parameter	*n* (%)	Model 1 COR (95% CI)	*P*	Model 2 AOR (95% CI)	*P*
miR-27b					
<0.655	19 (26.4)	1		1	
≥0.655	53 (73.6)	0.114 (0.029–0.439)	0.002*	0.022 (0.002–0.227)	0.001*
PPARα mRNA					
<1.309	44 (61.1)	1		1	
≥1.309	28 (38.9)	5.800 (2.013–16.715)	0.001*	5.376 (1.389–20.811)	0.015*
PPARγ mRNA					
<1.065	33 (45.8)	1		1	
≥1.065	39 (54.2)	3.571 (1.346–9.475)	0.011*	3.678 (1.075–12.580)	0.038*

Model 1 represented unadjusted confounding factors; Model 2 was adjusted for fetal sex, gestational age and weight gain during pregnancy. COR was crude OR value and AOR was adjusted OR value. miR-27b, PPARα and PPARγ were divided according to the cut-off value obtained from the receiver operating curve (ROC); gestational age was a continuous variable; gestational weight gain was divided according to the latest weight gain recommendation from the Institute of Medicine guidelines (IOM (2009)).
*$P < 0.05$.

macrosomia group was significantly lower than that of the control group. A cross-sectional study found that, compared with the control group, miR-34a and miR-27b expression levels in maternal plasma during the second trimester of macrosomia were significantly reduced.[20] The expression level of miR-27b in plasma of pregnant women with fetal growth restriction at <32 weeks of gestation age was higher than that of normal fetal mothers at the same gestation age.[24] Our study also observed that, among the three miRNAs detected in the placenta, only miR-27b was efficiently down-regulated, but miR-17 and miR-34a had a decreased trend in the macrosomia group. In addition, after adjusting for confounding factors such as infant sex, gestational age, and gestational weight gain, low miR-27b expression still elevated the risk of macrosomia. Besides, we confirmed by HTR8-SVneo cell experiments that miR-27b could negatively regulate PPARα and PPARγ protein expression levels without change in *PPARα* and *PPARγ* mRNA expression, indicating the involvement of post-transcription regulation.

This study also has some limitations. First, as a hospital-based case–control study, it may have some selection bias. However, the hospital selected in this study was a large general hospital with a wide coverage of pregnant women and the samples were collected continuously for 1 year, so it could be considered representative to a certain extent. Second, the small sample size led to relatively large CIs and decreased accuracy of the result. Accordingly, further study are required to expand the study population size for revealing the relation between placental PPARα/γ or miR-27b and non-GDM macrosomia.

In conclusion, low expression of miR-27b as well as high expression of *PPARα* and *PPARγ* mRNA in the placenta increased the risk of fetal macrosomia. miR-27b probably promote the occurrence of macrosomia through regulating PPARs. However, the detailed molecular mechanism by how miR-27b affects PPARs on non-GDM macrosomia needs to be further explored.

DATA AVAILABILITY

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

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AUTHOR CONTRIBUTIONS

X.-J.Y. conceived and designed the study. L.-F.N. conducted experiments and drafted the manuscript. Y.H. conducted experiments and collected the data. Y.-H.W. collected the placenta tissue samples. S.-S.W. and X.-J.L. collected the data and conducted the statistical analyses. H.-T.Y. critically revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from all participants included in the study.

ADDITIONAL INFORMATION

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