Original Article

miR-1233 and hypoxia inducible factor-1α in the placentas of patients with pregnancy-induced hypertension

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Abstract: Objective: To investigate the expressions of miR-1233 and hypoxia-inducible factor-1 alpha (HIF-1α) in the placentas of patients with hypertension of pregnancy (PIH) and the corresponding clinical values. Methods: Placentas were collected from 186 pregnant women with PIH and from 60 normal pregnant women during the same period. In terms of the severity of PIH, 63 collected placentas were assigned to the PIH group, 69 were assigned to the mild preeclampsia group, and 54 were assigned to the severe preeclampsia group. According to the pregnancy outcomes, 139 of the pregnant patients had normal pregnancy outcomes and 107 had adverse pregnancy outcomes. The relative expressions of miR-1233 and HIF-1α were investigated. Results: The more severe the PIH in patients, the higher the relative expressions of miR-1233 and HIF-1α in their placentas (P<0.05). The incidence of adverse pregnancy outcomes was higher in pregnant women with PIH than in those with normal pregnancy outcomes, and the incidence of adverse pregnancy outcomes increases with the severity of PIH (all P<0.05). Further research reveals that the relative miR-1233 levels and overall positivity rates of HIF-1α in the placentas of patients with adverse pregnancy outcomes were higher than those in the placentas of patients with normal pregnancy outcomes (all P<0.001). The adverse pregnancy outcomes and relative miR-1233 levels were positively correlated (r=0.585, P<0.001), and there was also a positive correlation between adverse pregnancy outcomes and HIF-1α expression (r=0.502, P<0.001). Conclusion: The miR-1233 and HIF-1α levels are elevated in the placentas of patients with PIH, and the adverse pregnancy outcomes are positively correlated with the elevated miR-1233 and HIF-1α levels in the placentas of such patients.

Keywords: Pregnancy-induced hypertension, miR-1233, hypoxia inducible factor 1α, clinical value

Introduction

Pregnancy-induced hypertension (PIH) is the most common complication of pregnant women during pregnancy. The incidence of PIH is high, up to 7% to 10%, and it is also the most important factor for maternal and fetal mortality [1, 2]. The worsening of PIH may lead to positive albuminuria, which is clinically called mild preeclampsia. If the disease further worsens, other organ damage may occur throughout the body, leading to severe mild preeclampsia [3]. Although the incidence of PIH is high clinically, its pathogenesis and etiology are still unknown [4]. Previous studies suggest that PIH may be associated with trophoblast invasion, endothelial dysfunction, inflammatory cytokines, or other factors [5, 6].

In recent years, with the development of gene detection technology, studies have shown that some related non-coding microRNAs (miRNA) can up-regulate or down-regulate post-transcriptional genes [7, 8]. In addition, miRNAs are closely associated with embryonic development and cell differentiation [9]. Placental dysfunction is a primary cause for the development of PIH. Further exploration reveals that disorders of trophoblast cells are closely related to placental dysfunction. A decline in the proliferation, migration, and invasion of trophoblast cells ultimately results in the presence of pla-
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cental dysfunction [10]. A growing number of studies indicate that the miRNAs in the placentas of patients with PIH are expressed differently from those in the placentas of normal pregnant patients [11, 12]. A finding from a previous study shows that miR-1233 plays an important role in the replication of human cells, DNA repairing, and the generation and metastasis of inflammatory cells [13]. In another study, the expression of miR-1233 was found to be up-regulated in most autoimmune diseases [14]. Moreover, miR-1233 also takes the corresponding control of cells by regulating proteins, growth factor signaling, and related receptors, and it has a key role in cell proliferation and differentiation [15]. Prior studies demonstrate that miR-1233 is abnormally expressed in patients with cardiovascular diseases and tumors [16, 17]. In patients with a normal pregnancy, miR-1233 is normally expressed in the trophoblast cells of the placentas. However, in patients with PIH, miR-1233 is abnormally expressed in the trophoblast cells of the placentas. As a result, the patients have higher blood pressure and develop albuminuria, and miR-1233 is abnormally expressed in the trophoblast cells of the placentas [17, 18].

Hypoxia-inducible factor-1 alpha (HIF-1α) is a regulator of oxygen homeostasis in human cells [19]. According to previous studies, HIF-1α plays a crucial role in the progression of ischemic heart disease, heart failure, and tumors [20, 21]. Some clinical studies indicate that blood pressure returns to normal and the clinical symptoms resolve rapidly after delivery in PIH patients, so researchers hold that the presence and development of PIH is associated with the superficial implantation of trophoblast cells and the impairment of endothelial cells in the placenta. At the early stage of placental formation, the environment is relatively hypoxic, so the activation of HIF-1α is necessary to promote the transcription of vascular endothelial growth factors. The superficial implantation of trophoblast cells causes a disorder of the vascular remodeling, which results in a reduced secretion of vasoactive substances and subsequent damage to the vascular endothelium. This ultimately leads to the presence of ischemia and to hypoxia of the placenta, inducing the onset of PIH [22].

As the pathogenesis of PIH remains unknown, by determining the differences in the miR-1233 and HIF-1α expressions in the placentas of PIH subjects, this study aimed to explore the effects and clinical values of miR-1233 and HIF-1α in the pathogenesis of PIH, and to further delve into the correlations between miR-1233 and HIF-1α expressions and the different pregnancy outcomes, with an aim to provide more referential evidence for the clinical research of PIH. Here we report as follows.

Materials and methods

General data

The clinical data and placenta samples were collected from 186 PIH pregnant women admitted to the Obstetrics and Gynecology Department in Qujing Maternal and Child Health Hospital from March 2017 to March 2019. The women varied in age from 21 to 39 years old. In addition, 60 women with normal pregnancies admitted to the hospital during the same period were enrolled as controls, and they were between 22 and 38 years old. The placentas of the enrolled patients were collected after delivery. Based on the severity of the disease, 63 of the collected placentas were assigned to the PIH group, 69 to the mild preeclampsia group, 54 to the severe preeclampsia group, and 60 to the control group. According to the different pregnancy outcomes, the pregnant women were classified as having normal pregnancy outcomes (139) or as having adverse pregnancy outcomes (107). The relative miR-1233 levels and the results of the HIF-1α measurement were observed in the placentas in different groups and in the patients with different pregnancy outcomes. All the above subjects signed and provided informed consent, and this study was approved by the Hospital Ethics Committee of Qujing Maternal and Child Health Hospital.

Inclusion and exclusion criteria

Inclusion criteria: the disease met the criteria for the diagnosis of PIH developed by the Hypertensive Disease Group, Obstetrics and Gynecology Branch of the Chinese Medical Association in 2012 [23]; the adverse pregnancy outcomes included: fetal distress, polyhydramnios, preterm low birth weight infants, and postpartum hemorrhage; pregnant women aged 18 years or above; singleton pregnancy; samples of placental tissues were collected from all the patients after delivery in the hospital and stored in the refrigerator at -80°C.
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Exclusion criteria: inability to cooperate in the study due to mental illness; severe disease in the heart, liver, or kidney; patients with hyperthyroidism, diabetes mellitus, autoimmune diseases, or tumors during pregnancy; critically-ill patients with less than one-year survival.

**Determination of the miR-1233 mRNA levels**

A placental tissue specimen (0.5 g) was taken out from the refrigerator at -80°C and sliced into 2-3 mm² sections. Trizol kits (Molecular Research Center, USA) were used for this study, and extracts of upstream and downstream primers were provided by the Guangzhou Rainbow Biotechnology Company [24]. A reverse transcription-polymerase chain reaction (RT-PCR) was performed to reversely transcribe the miRNA to cDNA with the use of a reverse transcription kit (Fermentas, Canada). cDNA was used as a template to amplify the DNA. Finally, the expression levels of the miR-1233 in the placental tissue samples were determined using quantitative PCR with fluorescent probes. The miRNA was reversely transcribed into cDNA with the use of the reverse transcription kits (Fermentas). The PCR reaction was performed using a PCR amplifier (Bio-Rad, USA). The primer sequences for the PCR-based amplification were as follows: 5'-GGGACATGAGAGCTGCCA-AC-3' and 5'-CCAGCAGCATGTCGAAGATC-3'. The cycle system (25 μL) was SYBR premix (2X, 12.5 μL), target gene-generated upstream and downstream primers (0.5 μL, respectively), cDNA template (2.0 μL), and ddH₂O (9.5 μL). The reaction conditions were pre-denaturation at 94°C for 4 min, at 95°C for 40 s, 60°C for 30 s, and 72°C for 30 s, 35 cycles in total, followed by an extension at 72°C for 1 min. The relative expression, taking the relative U6 snRNA level as a standard, was analyzed using the 2⁻ΔΔCt method. Finally, the relative miRNA-1233 level was determined.

**HIF-1α detection**

The specimens of the placental tissues were fixed with a formaldehyde solution, dehydrated, made transparent with ethanol (Shandong Hongda Biotechnology, China) and xylene (Shanghai Ruijian Biotechnology, China), and then embedded in paraffin. The paraffin-embedded specimens were sliced into 2-3-μm-thick sections. The HIF-1α polyclonal antibodies and kits used in this study were purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. (Beijing, China). The expression of HIF-1α protein was assayed using streptavidin-peroxidase (SP) immunohistochemistry. The specific procedures were as follows: first, the tissue specimens were hydrated with a gradient ethanol solution and a phosphate buffer saline (PBS) solution (Shandong Hongda Biotechnology, China) at 0.01 mol/L and pH 7.4 was added dropwise to the sections to cover the sections completely. The sections were placed on the slide and washed with PBS at 0.01 mol/L pH 7.4. Then heat-mediated antigen retrieval was performed at a high temperature and pressure. After the addition of the goat serum, primary and secondary antibodies (Shanghai Wheat Warehouse Biological Technology, China) were added dropwise to the sections. Twelve hours later, the DAB technique was used for the chromogenic reaction. The sections were washed with clean water, dehydrated in gradient ethanol, and ultimately mounted on the slides with xylene (Figure 1). HIF-1α positivity was defined in accordance with adjudication for the percent of positive cells observed under a microscope with five, random high power lenses, with <5% scored as 0, negative; 5-25% scored as 1, +; 26-50% scored as 2, ++, and 51-100% scored as 3, +++ [25].

**Statistical analysis**

The statistical analyses were performed using SPSS statistical software, version 17.0. Continuous variables were expressed as the mean ± standard deviation (X ± sd). The continuous variables with normal distributions and homogeneity of variance were measured using t tests, but those without normal distributions or homogeneity of variance were determined using rank sum tests and represented by Z. Count data were expressed as percentages and examined by Pearson’s chi-squared tests and Fisher’s exact probability tests, represented by chi-square. Differences with a P value less than 0.05 were considered to be statistically significant.

**Results**

**General and baseline data of patients**

There were significant differences in systolic and diastolic blood pressure across the PIH group, the mild preeclampsia group, the severe
miR-1233 and HIF-1α in the placentas of patients with pregnancy-induced hypertension

Comparisons of the relative miR-1233 levels across the four groups reveal that the relative miR-1233 levels in the PIH group, the mild preeclampsia group, and the severe mild preeclampsia group were higher than they were in the control group, and they were statistically different (P<0.05). The relative miR-1233 level was higher in the mild preeclampsia group than in the mild preeclampsia group and the PIH group (P<0.05); the relative miR-1233 level was higher in the severe mild preeclampsia group than in the mild preeclampsia group and in the control group, and they were statistically different (P<0.01). The rates of preterm low birth weight infants was higher in the severe mild preeclampsia group than it was in the PIH group and the mild preeclampsia group, and they were statistically different (P<0.01). The rates of polhydramnios were higher in the mild preeclampsia group and the severe mild preeclampsia group than in the control group, and the rate was higher in the severe mild preeclampsia group than in the PIH group and the mild preeclampsia group, and they were statistically different (P<0.01). The total incidence of adverse pregnancy outcomes in the PIH group, mild preeclampsia group, and severe mild preeclampsia group were higher than they were in the control group; the total incidence was higher in the severe mild preeclampsia group than it was in the PIH group and mild preeclampsia groups; it

Relative miR-1233 levels in patients

Comparisons of the relative miR-1233 levels across the four groups reveal that the relative miR-1233 levels in the PIH group, the mild preeclampsia group, and the severe mild preeclampsia group were higher than they were in the control group, and they were statistically different (P<0.05); the relative miR-1233 level was higher in the severe mild preeclampsia group than in the mild preeclampsia group and the PIH group (P<0.05); the relative miR-1233 level was higher in the mild preeclampsia group than in the PIH group (P<0.05), as shown in Table 2 and Figure 2.

HIF-1α levels in the patients

Comparisons of the HIF-1α measurements across the four groups show differences in the positivity of the HIF-1α measurements (P<0.001). For measurement of overall positivity of HIF-1α, the overall positivity rates of HIF-1α in the PIH group, mild preeclampsia group, and severe mild preeclampsia group were higher than they were in the control group, and they were statistically different (P<0.001). The overall positivity rates were lower in the PIH and mild preeclampsia groups than in the severe mild preeclampsia group, and they were statistically different (P<0.01; Table 3).

Adverse pregnancy outcomes in patients

The pregnancy outcomes of patients were compared among the four groups, and significant differences were found in the rates of fetal distress, preterm low birth weight infants, polhydramnios, and postpartum hemorrhage (all P<0.001). The rates of fetal distress in the PIH group, mild preeclampsia group, and severe mild preeclampsia group were higher than they were in the control group; the rate in the PIH group was higher than it was in the control group, and they were statistically different (P<0.01). The rate of preterm low birth weight infants was higher in the severe mild preeclampsia group than in the PIH group and the control group, respectively (both P<0.05); the rates of polhydramnios were higher in the mild preeclampsia group and the severe mild preeclampsia group than in the control group, the rate was higher in the severe mild preeclampsia group than it was in the PIH group and the mild preeclampsia group, and they were statistically different (P<0.01). The rates of postpartum hemorrhage in the mild preeclampsia group and the severe mild preeclampsia group were higher than they were in the control group, and the rate was higher in the severe mild preeclampsia group than it was in the PIH group and the mild preeclampsia group, and they were statistically different (P<0.001). The total incidence of adverse pregnancy outcomes in the PIH group, mild preeclampsia group, and severe mild preeclampsia group were higher than they were in the control group; the total incidence was higher in the severe mild preeclampsia group than it was in the PIH and mild preeclampsia groups; it

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Sex (male/female)</th>
<th>BMI</th>
<th>Parity</th>
<th>Mode of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild preeclampsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe mild preeclampsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative miR-1233 levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>PIH</td>
<td></td>
</tr>
<tr>
<td>Mild preeclampsia</td>
<td></td>
</tr>
<tr>
<td>Severe mild preeclampsia</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. HIF-1α detection. A. HIF-1α expression in the placentas of the normal pregnancy group; B. HIF-1α expression in the placentas of the pregnancy induced hypertension group; C. HIF-1α expression in the placentas of the mild preeclampsia group; D. HIF-1α expression in the placentas of severe preeclampsia group.
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Table 1. Comparison of the general and baseline data of the four groups

<table>
<thead>
<tr>
<th>Project</th>
<th>Pregnancy induced hypertension group (n=63)</th>
<th>Mild preeclampsia group (n=69)</th>
<th>Severe preeclampsia group (n=54)</th>
<th>Control group (n=60)</th>
<th>X^2/F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.7±5.1</td>
<td>28.0±5.2</td>
<td>28.2±5.0</td>
<td>27.4±5.1</td>
<td>0.264</td>
<td>0.852</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>152.17±7.19 *</td>
<td>153.01±6.22 *</td>
<td>163.00±8.27 *</td>
<td>125.20±7.35</td>
<td>294.193</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>89.44±6.77 *</td>
<td>90.00±5.50 *</td>
<td>94.28±6.51 *</td>
<td>70.40±5.24</td>
<td>185.226</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>27.48±1.14 *</td>
<td>27.38±2.25 *</td>
<td>27.17±1.97 *</td>
<td>27.55±1.18</td>
<td>0.337</td>
<td>0.799</td>
</tr>
<tr>
<td>Gestational week (w)</td>
<td>38.4±1.8</td>
<td>38.4±1.7</td>
<td>38.3±1.7</td>
<td>38.4±1.7</td>
<td>0.035</td>
<td>0.991</td>
</tr>
<tr>
<td>Parity (primiparity/multiparity)</td>
<td>45/18</td>
<td>47/22</td>
<td>39/15</td>
<td>40/20</td>
<td>0.589</td>
<td>0.899</td>
</tr>
<tr>
<td>Ways of giving birth (eutocia/caesarean birth)</td>
<td>39/24</td>
<td>40/29</td>
<td>31/23</td>
<td>35/25</td>
<td>0.317</td>
<td>0.957</td>
</tr>
</tbody>
</table>

Note: * indicates compared to the control group, * indicates compared to the severe preeclampsia group, P<0.05.

Table 2. Comparison of the relative miR-1233 levels in patients

<table>
<thead>
<tr>
<th>Project</th>
<th>Pregnancy induced hypertension group (n=63)</th>
<th>Mild preeclampsia group (n=69)</th>
<th>Severe preeclampsia group (n=54)</th>
<th>Control group (n=60)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative expression of miR-1233</td>
<td>1.594±0.539 ***</td>
<td>2.805±0.578 ***</td>
<td>3.693±1.139 ***</td>
<td>0.517±0.034</td>
<td>248.41</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: *** indicates P=0.001 compared to the control group; *** indicates P=0.001 compared to severe preeclampsia group; *** indicates P=0.001 compared to mild preeclampsia group.

Figure 2. Comparison of the relative miR-1233 levels in the four groups. * indicates compared to the control group, *** indicates P<0.001; # indicates compared to the severe preeclampsia group, ### indicates P<0.001; @ indicates compared to the mild preeclampsia group, @@ indicates P<0.001.

was also higher in the mild preeclampsia group than in the PIH group (Table 4).

Comparison of relative miR-1233 levels and HIF-1α measurements in patients with different pregnancy outcomes

Further comparisons between patients with adverse pregnancy outcomes and those with normal pregnancy outcomes indicate that the relative miR-1233 levels in patients with adverse pregnancy outcomes were higher than they were in patients with normal pregnancy outcomes, and they were statistically different (P<0.001). The HIF-1α positivity rates were different between the patients with adverse pregnancy outcomes and those with normal pregnancy outcomes, and the patients with adverse pregnancy outcomes had higher overall positivity rates of HIF-1α (P<0.001; Tables 5 and 6).

Correlations between adverse pregnancy outcomes and expression of miR-1233 and HIF-1α

Findings of investigating the correlation between adverse pregnancy outcomes and the relative miR-1233 levels show that r was equal to 0.585 (P<0.001), and the adverse pregnancy outcomes were positively correlated to the relative miR-1233 levels. For the results from the investigation of the correlation between adverse pregnancy outcomes and HIF-1α expression, r was equal to 0.502 (P<0.001). There was a positive correlation between adverse pregnancy outcomes and HIF-1α expression.

Discussion

In the pathogenesis of hypertension, miR-1233 activates the renin-angiotensin-aldosterone system (RAAS), stimulates aldosterone secretion, and causes an increase in water-sodium reten-
miR-1233 and HIF-1α in the placentas of patients with pregnancy-induced hypertension

Table 3. Comparison of the HIF-1α levels in the four groups

<table>
<thead>
<tr>
<th>HIF-1α</th>
<th>-</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>Total positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy induced hypertension group (n=63)</td>
<td>14 (22.22)</td>
<td>27 (42.86)</td>
<td>18 (28.57)</td>
<td>4 (6.35)</td>
<td>77.78%***###</td>
</tr>
<tr>
<td>Mild preeclampsia group (n=69)</td>
<td>9 (13.04)</td>
<td>19 (27.54)</td>
<td>25 (36.23)</td>
<td>16 (23.19)</td>
<td>86.95%***##</td>
</tr>
<tr>
<td>Severe preeclampsia group (n=54)</td>
<td>0 (0.00)</td>
<td>10 (18.52)</td>
<td>25 (46.30)</td>
<td>19 (35.19)</td>
<td>100.00%***</td>
</tr>
<tr>
<td>Control group (n=60)</td>
<td>34 (56.67)</td>
<td>18 (30.00)</td>
<td>8 (13.33)</td>
<td>0 (0.00)</td>
<td>43.33%</td>
</tr>
</tbody>
</table>

X² 89.666 58.108
P <0.001 <0.001

Note: Compared to the control group, ***indicates P<0.001; compared to the severe preeclampsia group, ##indicates P<0.01; ###indicates P<0.001.

Table 4. Comparison of the adverse pregnancy outcomes in the four groups

<table>
<thead>
<tr>
<th>Adverse pregnancy outcomes</th>
<th>Fetal distress</th>
<th>Premature low birth weight infants</th>
<th>Hydramnios</th>
<th>Postpartum hemorrhage</th>
<th>Total incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy induced hypertension group (n=63)</td>
<td>8 (12.79)**</td>
<td>6 (9.52)*</td>
<td>7 (11.11)***</td>
<td>9 (14.28)***</td>
<td>20 (31.7%)***###</td>
</tr>
<tr>
<td>Mild preeclampsia group (n=69)</td>
<td>14 (20.29)***</td>
<td>10 (14.49)</td>
<td>12 (17.39)***</td>
<td>18 (26.08)***###</td>
<td>36 (52.17%)***###</td>
</tr>
<tr>
<td>Severe preeclampsia group (n=54)</td>
<td>19 (35.19)***</td>
<td>24 (44.44)***</td>
<td>26 (48.14)***</td>
<td>47 (87.03%)***###</td>
<td></td>
</tr>
<tr>
<td>Control group (n=60)</td>
<td>1 (1.67)</td>
<td>2 (3.33)</td>
<td>2 (3.33)</td>
<td>3 (5.00)</td>
<td>4 (6.67%)</td>
</tr>
</tbody>
</table>

X² 23.927 13.736 35.904 33.568 80.442
P <0.001 <0.001 <0.001 <0.001 <0.001

Note: Compared to the control group, *indicates P<0.05, **indicates P<0.01, ***indicates P<0.001; compared to the severe preeclampsia group, *indicates P<0.05, **indicates P<0.01, ***indicates P<0.001; compared to the mild preeclampsia group, **indicates P<0.01.

Table 5. Comparison of relative miR-1233 levels in patients with different pregnancy outcomes

<table>
<thead>
<tr>
<th>Project</th>
<th>Relative expression of miR-1233 (Adverse pregnancy outcomes n=107)</th>
<th>Normal pregnancy outcomes (n=139)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative expression of miR-1233</td>
<td>3.008±1.232</td>
<td>1.446±1.000</td>
<td>10.970</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 6. Comparison of the HIF-1α measurements in patients with different pregnancy outcomes

<table>
<thead>
<tr>
<th>HIF-1α</th>
<th>-</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>Total positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse pregnancy outcomes (n=107)</td>
<td>7 (22.22)</td>
<td>18 (42.86)</td>
<td>53 (28.57)</td>
<td>29 (6.35)</td>
<td>93.46%</td>
</tr>
<tr>
<td>Normal pregnancy outcomes (n=139)</td>
<td>50 (31.04)</td>
<td>56 (27.54)</td>
<td>23 (36.23)</td>
<td>10 (23.19)</td>
<td>64.03%</td>
</tr>
</tbody>
</table>

X² 70.074 29.414
P <0.001 <0.001

As for HIF-1α, previous studies have demonstrated that HIF-1α is normally secreted in the placentas of normal pregnant women, but it is abnormally expressed in the placentas of PIH pregnant women. In addition, the quality and quantity of the angiogenesis of the placenta in patients with a normal HIF-1α expression are superior to those with an abnormal HIF-1α expression. Therefore, HIF-1α may be abnormally expressed in PIH pregnant patients [27]. One study revealed that the up-regulation of HIF-1α expression is accompanied by up-regulated P53 gene expression. The P53 gene promotes the apoptosis of placenta cells and inhibits tissue repair, which might be related to the fact that the up-regulation of HIF-1α in the placentas of PIH patients leads to further...
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aggravation of PIH [28]. Another study suggested that the inhibition of HIF-1α expression up-regulates the expression of endothelial growth factor, which improves the erythrocyte oxygen carrying capacity in the blood, alleviates ischemia-induced tissue damage, and promotes angiogenesis [29, 30]. Our current study revealed that for pregnant patients with PIH, the HIF-1α positivity rates in the placenta tissues increase with the severity of PIH, which is consistent with the results of the above-mentioned studies.

Hypertension during pregnancy tends to increase the incidence of adverse pregnancy outcomes. Previous studies demonstrate that PIH is frequently accompanied by adverse pregnancy outcomes such as fetal distress, growth restriction, premature delivery and postpartum hemorrhage [31, 32]. Likewise, in our present study, we found that the more severe PIH in pregnant women, the higher the incidence of adverse pregnancy outcomes, which is consistent with the findings from the above-mentioned studies. Further research on adverse pregnancy outcomes and the expressions of miR-1233 and HIF-1α proved that the relative miR-1233 levels and the positivity rates of HIF-1α in patients with adverse pregnancy outcomes were significantly higher than they were in patients with normal pregnancy outcomes. This might be related to the fact that in the above expired mechanisms, up-regulated miR-1233 and HIF-1α expressions result in increased blood pressure and the occurrence of placental ischemia and hypoxia, which induces the presence of adverse outcomes [26, 29]. Thus, in the treatment of PIH pregnant women, intervening in the expressions of miR-1233 and HIF-1α is feasible, as it has a certain effect and a clinical value in reducing the incidence of adverse pregnancy outcomes.

As the sample size of our present study was relatively small, we should expand the sample size in further research. In addition, further studies are required to explore the mechanisms affecting miR-1233 and HIF-1α in pregnant women with PIH.

In conclusion, miR-1233 and HIF-1α expressions in the placentas of pregnant patients with PIH are elevated, and there are correlations between the incidence of adverse pregnancy outcomes and miR-1233 and HIF-1α expressions.

Disclosure of conflict of interest
None.

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