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Original Research

Exploration on the relationship between hypoxia inducible factor-1α and morbidly adherent placenta

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Summary

Objective: This study aims to explore the role of hypoxia inducible factor-1α (HIF-1α) in morbidly adherent placenta (MAP). *Materials and Methods*: Ten pregnant women with placenta increta, 20 pregnant women with placenta previa, and 30 normal pregnant women as controls participated in the present study. Real-time reverse transcription polymerase chain reaction (RT-PCR) was used to measure the mRNA expression of HIF-1α in the placenta. Enzyme-linked immunosorbent assay (ELISA) was performed to analyze the HIF-1α protein levels in the placenta. *Results*: The mean expression of placental HIF-1α in the placenta increta and placenta previa groups was significantly higher than that in the normal placenta. The level of placental HIF-1α in the placenta increta was significantly higher than that in the placenta previa ($p < 0.05$). The level of placental HIF-1α had no obvious correlation with the accreta site and umbilical cord insertion. *Conclusion*: The morbidly of adherent placenta is closely correlated to adverse pregnancy outcomes during the perinatal period. Placental HIF-1α is associated with morbidly adherent placenta.

Key words: HIF-1α; Placenta increta; Placenta previa; Pathogenesis; Morbidly adherent placenta.

Introduction

Abnormalities associated with morbidly adherent placenta can be reflected in the abnormal site, such as the placenta previa (PP), and depth, such as the placenta accreta (PA), of adherence. This refers to a group of diseases of abnormal adherence of the placenta to the uterine wall. Morbidly adherent placenta seriously affects maternal and child health. The change in microenvironment from hypoxia to normoxia (or the physiological shift in oxygen pressure) is a prerequisite for the normal development of the placenta. The transcription factor HIF-1 was found in nuclear extracts under the conditions of oxygen deficit. Under hypoxic conditions, its expression changes along with the changes in intracellular oxygen concentration. The present study investigates the expression level of HIF-1 in cases of morbidly adherent placenta, in order to determine its relationship with the pathology.

Clinical Significance

The present study investigates the expression level of HIF-1 in cases of morbidly adherent placenta, in order to determine its relationship with the pathology. By mediating EMT and VEGF, HIF-1α can enhance the trophocyte invasion, leading to abnormal vascular remodeling, and drive the genesis and development of the PA. However, the occurrence of MAP is complicated. At present, the pathophysiological mechanism of MAP is not yet fully understood. The specific role of HIF-1α in the genesis and development of MAP requires further studies.

Methods

From January to December 2015, the investigators reviewed pregnant women who received regular antenatal care, and were hospitalized for caesarean section at the Obstetric Department of Fujian Provincial Maternity and Children's Hospital. All subjects were ethnic Chinese. Based on the clinical manifestations, ultrasound test and postoperative pathological examination, there were 10 cases of PA and 20 cases of PP. Thirty pregnant women who received caesarean section due to scarred uterus, abnormal fetal site, abnormal obstetric canal, and social factors were selected and assigned to the normal control group (NC). For the diagnostic criteria for PA and PP, the present study referred to a relevant literature [1]. Late pregnancy was defined as 28 weeks or later. Those with both PP and PA were included in the PA group. None of the subjects underwent labor, or had premature rupture of membranes at the time of their caesarean section. Furthermore, none of the women were in active labor, had rupture of the fetal membranes, or had clinical signs of infection. Patients with pregnancy complications and surgical complications were excluded from the study. All subjects were single pregnancies. An informed consent was obtained from each patient. The protocol for the present study was approved by the local Institutional Review Board. The clinical features of the subjects are presented, as follows:

Collection of specimen

After the placenta was delivered, the tissues were aseptically taken from the maternal surface of the placenta. The specific sites for collecting the tissues of different groups

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Table 1. — *Comparison of clinical data in the three groups (mean ± SD).*

Group	No. of cases	Age (Y)	No. of pregnancies	No. of cesarean sections	Time between the xurrent and the previous cesarean sections (Y)	Gestational weeks
PA group	10	31.7 ± 6.6	2.7 ± 1.8*★	0.7 ± 0.7	3.7 ± 4.0	35.3 ± 4.0*
PP group	20	30.3 ± 5.8	1.5 ± 1.5	0.4 ± 0.8	1.9 ± 3.5	36.2 ± 2.5*
Normal group	30	30.2 ± 3.8	1.0 ± 0.8	0.5 ± 0.6	2.1 ± 2.5	39.2 ± 1.1

Note: Compared with the normal group, *$p < 0.05$; compared with the PP group, ★ $p < 0.05$.

Table 2. — *Comparison of clinical data of pregnant women in the three groups (mean ± SD).*

Group	No. of cases	Hospital stay	Hospital costs (in Unit: RMB 10,000)	Intraoperative hemorrhage (mL)	Postoperative hemorrhage (mL)	Duration of operation (min)
PA group	10	8.0 ± 4.3*	2.2 ± 1.6*★	1280.0 ± 1316.9*★	768.4 ± 793.3*	92.6 ± 67.6*★
PP group	20	6.5 ± 2.9	1.2 ± 0.3	543.0 ± 179.7	574.8 ± 177.8	54.8 ± 15.9
Normal group	30	5.4 ± 1.7	0.9 ± 0.1	383.3 ± 130.9	400.2 ± 135.6	53.8 ± 16.9

Note: Compared with the normal group, *$p < 0.05$; compared with the PP group, ★$p < 0.05$.

are described, as follows: PA group: The placenta tissues were collected from two sites, the accreta site and the non-accreta site. PP group: The placenta tissues were collected from two sites: the marginal site and the central site. NC group: The placenta tissues were collected from one site: the central site. The size of each tissue collected was 1.0 × 1.0 × 1.0 cm. Any site with hemorrhage, necrosis, or calcification were avoided. After being fully rinsed by normal saline, the tissues were dried with sterile gauze. Then, these were placed in sterile PV tubes, and stored in a freezer at -80 °C. Repeated freezing and thawing was avoided.

ELISA and RTQ-PCR were adopted to detect the protein and mRNA expression of HIF-1α in the placenta tissues in the PA, PP and normal groups.

Detection of the protein level of HIF-1α with ELISA

All reagents were purchased from Abcam, and used according to the instructions. Total protein was extracted from the tissues. Then, the reagents were used to measure the protein concentration of the samples. According to the steps in the instructions, the reagents were placed in 96-well plates, and incubated at 37 °C for 20 minutes. Then, a microplate reader (equipped with a quantitative analysis system) was used to measure the light absorption value at 450 nm.

Detection of the mRNA expression level of HIF-1α with RTQ-PCR

Trizol was used to extract the total RNA from the placenta tissues. A spectrophotometer was used to measure the light absorption values (A) at 260 nm and 280 nm. The total RNA concentration and purity were calculated, and the RNA integrity was determined by 1% agarose gel electrophoresis. The total RNA (2 μg) was taken and reverse transcribed into cDNA. Real-time fluorescence quantification PCR was used for the quantitative determination. The full-length sequence of the target gene mRNA was obtained from GenBank. Primer and probe design software Primer 5.0 was used to design the primer sequence. After the Blast analysis, the primer sequence revealed the necessary specificity. The present study entrusted Beijing Dingguo Changsheng Biotechnology Co., Ltd. to synthesize all the primers. β-actin: The upstream primer was 5'-ATC ATG TTT GAG ACC TTC AAC A-3', and the downstream primer was 5'-CAT CTC TTG CTC GAA GTC CA-3'. HIF-1α: The upstream primer was 5'-TGG ACA CTG GTG GCT CAC TA-3', and the downstream primer is 5'-ATG CTA CTG CAA TGC AAT GG-3'. The RT-PCR reaction conditions and procedures in the instructions were followed, and 2-△△CT was used to conduct relative quantitative analysis of the results.

Statistical analysis

All data were statistically processed using the SPSS 19.0 software package. Measurement data were expressed as mean ± standard deviation (x ± SD). Differences among groups were compared using one-way ANOVA. The comparison between two groups was performed using t-test or t' test. Inspection level α = 0.05, and $p < 0.05$ demonstrated statistical significance.

Results

Clinical data analysis of pregnant women in the three groups

The differences among patients in the PA, PP and NC groups, in terms of age, occupation, number of cesarean sections, and duration between the present and previous cesarean sections, were not statistically significant ($p > 0.05$). The hospital stay was longer, and the postoperative hemorrhage was significantly higher in the PA group than in the NC group ($p < 0.05$). However, the differences between the PA and PP groups and between the PP and NC groups had no statistical significance ($p > 0.05$). The number of pregnancies, the amount of intraoperative hemorrhage, and the duration of the cesarean section were higher in the PA group than in the PP and normal groups ($p < 0.05$). However, the differences between the PP and NC groups had no statistical significance ($p > 0.05$). The differences in terms of educa-

Table 3. — *Comparison of the clinical data of newborns in the three groups (mean ± SD).*

Group	No. of cases	Weight of newborn (g)	Apgar score	Placental weight (g)
PA group	10	2441.0 ± 913.7*	9.3 ± 1.3	511.0 ± 147.8*
PP group	20	2651.1 ± 644.7*	8.6 ± 2.0	577.8 ± 106.5*
Normal Group	30	3368.8 ± 528.6	8.2 ± 2.3	673.6 ± 147.3

Note: Compared with the normal group, $*p < 0.05$.

tion background, gestational weeks, and way of hospitalization between the PA and PP groups and the NC group were statistically significant ($p < 0.05$) (Tables 1 and 2).

Table 4. — *The protein expression levels of HIF-1α in placenta tissues in the three groups (mean ± SD).*

Group	No. of cases	Expression level of HIF-1α protein
PA group	10	0.388 ± 0.159*★
PP group	20	0.305 ± 0.116*
Normal group	30	0.242 ± 0.108

Note: Compared with the normal group, $*p < 0.05$; compared with the PP group, $★p < 0.05$.

Table 5. — *The mRNA expression level of HIF-1α in placenta tissues in the three groups (mean ± SD).*

Group	No. of cases	Expression level of HIF-1α mRNA
PA group	10	0.514 ± 0.273*★
PP group	20	0.382 ± 0.230*
Normal group	30	0.269 ± 0.191

Note: Compared with the normal group, $*p < 0.05$; compared with the PP group, $^{H}p < 0.05$.

Clinical data analysis of newborns in the three groups

The Apgar scores of newborns in the PA, PP and NC groups were not statistically significant ($p > 0.05$). The differences in terms of placental weight, weight of the newborn, and newborns transferred to the High Risk Observation Room, Neonatology Department, or the Neonatal Intensive Care Unit (NICU), between the PA and PP groups and NC group, indicated a statistical significance ($p < 0.05$). The premature birth rate in the PA group (50%, 5/10) and PP group (45%, 9/20) were significantly higher than that in the NC group (0%, 0/30). The differences were statistically significant ($p < 0.05$). However, the difference between the PA and PP groups had no statistical significance ($p > 0.05$) (Table 3).

Analysis of the expression of HIF-1α in placenta tissues in the three groups

The protein expression of HIF-1α was detected in the placenta tissues in the PA, PP and NC groups. The protein levels of HIF-1α were significantly higher in the PA and PP groups than in the NC group ($p < 0.05$). Furthermore, the protein level of HIF-1α was statistically higher in the PA group than in the PP group ($p < 0.05$) (Table 4 and Figure 1).

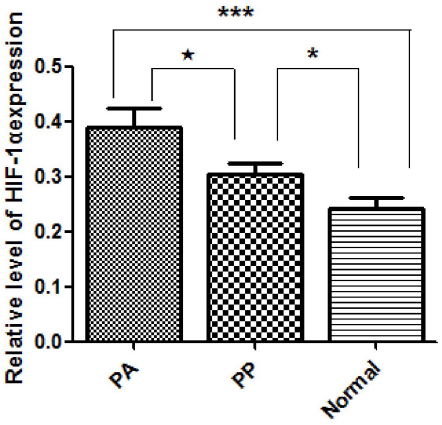

Figure 1. — The protein expression levels of HIF-1α in placenta tissues in the PA, PP and normal groups detected by ELISA. $***p < 0.001$ (PA *vs.* normal group), $*p < 0.05$ (PP *vs.* normal group), and $★p < 0.05$ (PA *vs.* PP groups).

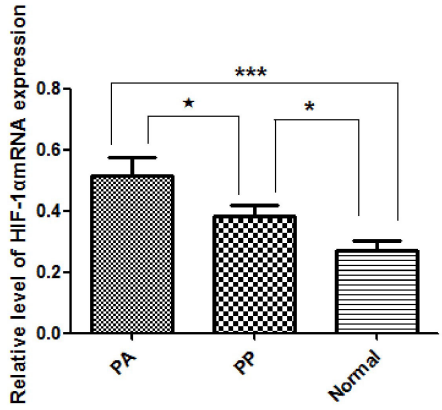

Figure 2. — The mRNA expression level of HIF-1α in placenta tissues in the PA, PP and normal groups detected by qRT-PCR. $***p < 0.001$ (PA *vs.* normal group), $*p < 0.05$ (PP *vs.* normal group), and $★p < 0.05$ (PA *vs.* PP groups).

Analysis of the mRNA levels of HIF-1α in placenta tissues in the three groups

The mRNA expression of HIF-1α was detected in placenta tissues in the PA, PP and NC groups. The mRNA levels of HIF-1α were significantly higher in the PA and PP

Table 6. — *The protein and mRNA expression levels of HIF-1α in placenta tissues collected from different sites in the PA group (mean ± SD).*

	Accreta site	Non-accreta site
ELISA	0.435 ± 0.190	0.341 ± 0.110
RTQ-PCR	0.564 ± 0.285	0.464 ± 0.266

Table 7. — *The protein expression level of HIF-1α in placenta tissues collected from different sites in the PP group (mean ± SD).*

	Central site	Marginal site
ELISA	0.294 ± 0.104	0.316 ± 0.129
RTQ-PCR	0.403 ± 0.227	0.361 ± 0.227

groups than in the NC group ($p < 0.05$). Furthermore, the mRNA expression level of HIF-1α was significantly higher in the PA group than in the PP group ($p < 0.05$) (Table 5 and Figure 2).

Analysis of the expression of HIF-1α in placenta tissues collected from different sites in the PA group

ELISA was used to detect the protein level of HIF-1α in placenta tissues collected from the accreta sites and non-accreta sites of PA patients. The results revealed that the difference in protein expression level of HIF-1α in placenta tissues collected from different sites in PA patients had no statistical significance ($p > 0.05$). The qRT-PCR was used to detect the mRNA expression level of HIF-1α in placenta tissues collected from the accreta sites and non-accreta sites in PA patients. The results reveald that the difference in the mRNA expression of HIF-1α in placenta tissues collected from different sites had no statistical significance ($p > 0.05$) (Table 6 and Figure 3).

Analysis of the expression of HIF-1α in placenta tissues collected from different sites in the PP group

ELISA was used to detect the protein expression level of HIF-1α in placenta tissues collected from the central site and marginal site in PP patients. The results revealed that the difference in the protein expression of HIF-1α in placenta tissues collected from different sites was not statistically significant ($p > 0.05$). The qRT-PCR was used to detect the mRNA level of HIF-1α in placenta tissues collected from the central and marginal sites in PP patients. The results revealed that there was no difference in the mRNA expression of HIF-1α in placenta tissues collected from different sites in the PP group ($p > 0.05$) (Table 7 and Figure 4).

Discussion

With the advance in surgical techniques, such as cesarean section and abortion, the morbidity of MAP has dramatically increased. This affects maternal and child health and, to some extent, even endangers the safety of mothers and infants.

Studies have revealed that the morbidity of PA rose from 0.8‰ (10/12, 890) between 2004 and 2010 to 1.5‰ (9/5, 948) between 2010 and 2014. Furthermore, the rate of hysterectomy caused by PA drastically increased from 20.0% (2/10) to 77.8% (7/9) [2]. Ahmed *et al.* [3] reported that 1.3% (52/3841) of pregnant women with delivery in the hospital in 2014 had PP. Those who had both PP and PA accounted for 26.4% (14/52), in which 15.1% received a hysterectomy, while 3.8% had consequent intestinal injury, 13.2% a bladder injury, 13.2% had stillbirth, and 20% of the newborns were transferred to the NICU. The presence of PA can cause adverse pregnancy outcomes, while increasing the hospital stay and economic burden [4].

The results of the present study also revealed that the number of pregnancies, hospitalization costs, hospital stay, intraoperative hemorrhage, postoperative hemorrhage, and duration of operations were significantly higher in the PA group than in the PP or NC groups. In addition, among the 10 patients with PA, one case (10%) received a hysterectomy, while 80% (8/10) of the pregnant women stayed in the intensive care unit (ICU). Furthermore, half (5/10) of the newborns were premature, 50% (5/10) of the newborns were transferred to the High Risk Observation Room, and almost a third (3/10) of the newborns were admitted to the Neonatology Department. Among the 20 patients with PP, 70% (14/20) of the pregnant women were admitted to the ICU, 45% (9/20) of the newborns were premature, 60% (12/20) of the newborns were transferred to the High Risk Observation Room, and 30% (6/20) of the newborns were admitted to the Neonatology Department. It can be observed that both PA and PP are serious complications in the late trimester of pregnancy, and that these are closely correlated to adverse pregnancy outcomes.

Morbidly adherent placenta severely threatens the safety of mothers and infants. However, there are few studies on its etiology and pathogenesis. At present, most studies hold that PA is due to a decidual defect, the excessive invasion of trophocytes, and abnormal blood vessel remodeling. The present study indicated that the protein and mRNA levels of HIF-1α in both the PA and PP groups were significantly higher than those in the NC group. Furthermore, the protein and mRNA expression of HIF-1α was higher in the PA group than in the PP group. It was speculated that the increase in HIF-1α expression leads to the increase in MAP. These decidual defects may cause the increase in HIF-1α expression, enhance the invasion by trophocytes, and affect vascular remodeling.

HIF-1α and decidual defects

HIF-1 is a transcription factor found in nuclear extracts under oxygen deficit conditions. Under hypoxic conditions, its expression changes along with the changes in intracellular oxygen concentration. In order to adapt to the hypoxic environment, the target genes of HIF-1α varies in different tissues. Under hypoxic conditions, HIF-1α becomes stable, interacts with a coactivator, such as cAMP/p300, and connects with the HIF-1 binding site (hypoxia response element) on the promoter or enhancer element of genes related

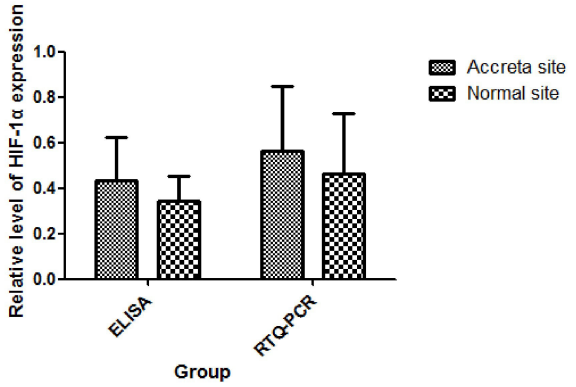

Figure 3. — The protein and mRNA expression of HIF-1α in placenta tissues collected from the accreta and non-accreta sites in PA patients detected by ELISA and qRT-PCR, showing no significant differences ($p > 0.05$).

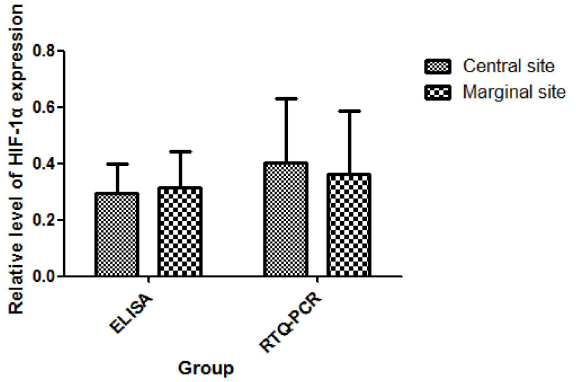

Figure 4. — The protein and mRNA expression of HIF-1α in placenta tissues collected from the central site and marginal site in PP patients detected by ELISA and qRT-PCR, showing no significant differences ($p > 0.05$).

to hypoxia adaption, such as vascular endothelial growth factor (VEGF), in order to form transcription initiation complexes, promote genetic transcription, and give full play to its biological activity. Through the increase in VEGF expression or the decrease in stromal cell-derived factor 1 (SDF-1) expression, HIF-1α participates in ESC decidualization in a low-oxygen environment. HIF-1α is the most critical factor for hypoxia response [5]. Tsuzuki *et al.* [6] cultured endometrial stromal cells *in vitro*, and measured the expression of HIF-1α and VEGF. They found that HIF-1α may affect the angiogenesis of the endometrium under hypoxic conditions.

Thurn *et al.* [7] reported that the morbidity of PA patients after cesarean section is nearly seven times higher than for those without a history of cesarean section. The morbidity of PA after three or more cesarean sections rose by 56 times. Multiple intrauterine operations may cause damage to the fundus of the endometrium and endometrial infection, leading to damage of epithelial cell regeneration and angiogenesis, followed by difficulty in endometrial repair. Endometrial repair is associated with the increase in VEGF expression, which is affected by HIF-1α. Hence, HIF-1α is involved in endometrial repair and regeneration [8]. During the subsequent pregnancy, the defect or lack of development of the endometrium with scarring may lead to a defect or maldevelopment of the decidua of the basal layer, the decrease in local oxygen pressure in placenta tissues, the promotion of HIF-1α expression, the enhancement of trophoblast invasion into the muscular layer that can even penetrate through the muscular wall, and the formation of PA. The present study revealed the increase in HIF-1α expression in placenta tissues in the PA and PP groups, indicating that the decidual defect can affect the regulation of HIF-1α expression. Furthermore, overexpression of HIF-1α may participate in MAP by affecting the decidualization.

HIF-1α and trophoblast invasion

A large number of studies at home and abroad have implied that there is an overexpression of HIF-1α in various tumor tissues, such as liver cancer, breast cancer, cervical cancer, thymic cancer and renal cancer, and that this has a vital role in maintaining the energy metabolism of cancer cells, neovascularization and metastasis. In the hypoxic microenvironment of tumor tissues, HIF-1α can regulate angiogenesis, cell proliferation and survival, and cell metabolism by promoting the expression of VEGF, IGF, TGF and glycolytic pathway-related enzymes, and play a key role in the genesis and development of tumors. The trophoblast cells in PA have a similar molecular mechanism to that of tumor cells during infiltration and invasion.

One crucial mechanism for hypoxia to participate in the invasion and metastasis of malignant tumors is the regulation of the epithelial-mesenchymal transition (EMT) of tumor cells. Through EMT, epithelial cells change their polarity, lose the phenotype connected with the basal membrane, and transform into the mesenchymal phenotype with high migration and invasion, and abilities of resistance to the apoptosis and degradation of the extracellular matrix. HIF-1α is an important factor for hypoxia-induced EMT, and PA trophoblast invasion is associated with EMT. The adhesion molecule E-CAD plays a significant role in maintaining cell stability, intercellular adhesion, and the regulation of polarity. The decrease in E-CAD expression can lead to an increase in abnormal cell adhesion and cell invasion [9]. Under continuous hypoxia, the mRNA and protein expression of E-CAD significantly decreases [10]. The EMT is also regulated by the VEGF expression [11], and VEGF is the target gene of HIF-1α. In the present study, the overexpression of HIF-1α in placenta tissues played a role in the PA and PP groups. Therefore, the overexpression of HIF-1α regulates EMT by mediating E-CAD, VEGF, and its receptors, further facilitating the invasion or proliferation of trophoblast cells, and participating in PA.

HIF-1α and vascular remodeling

PP along with PA are associated with the overexpression of VEGF, placenta growth factor (PIGF), and their receptors [12]. VEGF, PIGF and the receptors are important cy-

tokines for placental vascularization. All these factors are target genes of HIF-1α. There are no differences in terms of the expression of sFlt1, PIGF, sFlt1/PIGF ratio, and VEGF in plasma, between patients with PP and patients without abnormal placenta adherence [13]. The present study revealed the protein and mRNA overexpression of HIF-1α in placenta tissues obtained from PA and PP patients. In a study on preeclampsia, Maebayashi *et al.* [14] reported that the protein and mRNA expression of HIF-1α is negatively correlated with soluble fins-like tyrosine kinase receptor-1 (sFlt-1), but is positively correlated with PIGF. Trophoblast infiltration and abnormal vascular remodeling are involved in the pathogenesis of pre-eclampsia. Their study further explained that PA is associated with abnormal vascular remodeling. By comparing the expression level of sFlt-1 in placenta tissues in normal pregnancy, PA and PP, McMahon *et al.* [15] found that the PA group had a low sFlt-1 expression, which is correlated with the depth of invasion. Soluble fins-like tyrosine kinase receptor-1 is an antagonist of VEGF. After sFlt-1 binds to VEGF and PIGF, the signals of VEGF and PIGF cannot be transmitted into cells. Hence, VEGF and PIGF cannot exert their physiological functions. Soluble fins-like tyrosine kinase receptor-1 also has a strong anti-angiogenic effect. Therefore, the overexpression of HIF-1α may lead to vascular remodeling abnormalities through the upregulation of VEGF and PIGF, or the downregulation of sFlt-1, followed by the onset of PA.

Decidual defects lead to a hypoxic environment for placenta tissues, and promote the overexpression of HIF-1α. By mediating EMT and VEGF, HIF-1α can enhance the trophocyte invasion, leading to abnormal vascular remodeling, and drive the genesis and development of PA. The occurrence of MAP is complicated. At present, the pathophysiological mechanism of MAP is not yet fully understood. The specific role of HIF-1α in the genesis and development of MAP requires further studies.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Fujian Provincial Maternal and Child Health Hospital (approval number: 20140928).

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Conflict of Interest

The authors declare no conflict of interest.

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References

[1] Leveno K.J., Cunningham F.G., Alexander J.M., Bloom S.L., Casey B.M., Dashe J.S., *et al.*: "Williams Manual of Obstetrics: Pregnancy Complications, 22nd Edition". New York: McGraw-Hill Medical, 2007, 598 pages.

[2] Pan X.Y., Wang Y.P., Zheng Z., Tian Y., Hu Y.Y., Han S.H.: "A marked increase in obstetric hysterectomy for placenta accreta". *Chin Med J*, 2015, *128*, 2189-2193.

[3] Ahmed S.R., Aitallah A., Abdelghafar H.M., Alsammani M.A.: "Major placenta previa: rate, maternal and neonatal outcomes experience at a tertiary maternity hospital, sohag, egypt: a prospective study". *J Clin Diagn Res*, 2015, *9*, QC17.

[4] Mogos M.F., Salemi J.L., Ashley M., Whiteman V.E., Salihu H.M.: "Recent trends in placenta accreta in the United States and its impact on maternal-fetal morbidity and healthcare-associated costs, 1998-2011". *J Matern Fetal Neonatal Med*, 2015, *29*, 1077-1082.

[5] Maybin J.A., Nikhil H., Pamela B., Jabbour H.N., Critchley H.O.D.: "The regulation of vascular endothelial growth factor by hypoxia and prostaglandin F2α during human endometrial repair". *J Clin Endocrinol Metab*, 2011, *96*, 2475-2483.

[6] Tomoko T., Hidetaka O., Hisayuu C., Shoko T., Akemi N., Katsuhiko Y., *et al.*: "Hypoxic stress simultaneously stimulates vascular endothelial growth factor via hypoxia-inducible factor-1α and inhibits stromal cell-derived factor-1 in human endometrial stromal cells". *Hum Reprod*, 2012, *27*, 523-530.

[7] Matsubara S., Takahashi H., Takei Y., Lefor A.K.: "Re: Abnormally invasive placenta - prevalence, risk factors and antenatal suspicion: results from a large population-based pregnancy cohort study in the Nordic countries". *BJOG*, 2016, *123*, 1031-1032.

[8] Hidetaka O., Tomoko T., Hisayuu S., Akemi N., Katsuhiko Y., Hideharu K.: "Regulation of decidualization and angiogenesis in the human endometrium: mini review". *J Obstet Gynecol Res*, 2014, *40*, 1180-1187.

[9] Duzyj C.M., Buhimschi I.A., Motawea H., Laky C.A., Cozzini G., Zhao G., *et al.*: "The invasive phenotype of placenta accreta extravillous trophoblasts associates with loss of E-cadherin". *Placenta*, 2015, *36*, 645-651.

[10] Jing S., Xu Q., Jing S., Zhao Z., Zhao Z., Wu F., *et al.*: "Effect of silencing HIF-1Î ± by RNA interference on adhesion and invasion of the human nasopharyngeal carcinoma cell line CNE-1". *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*, 2015, *50*, 929-933. [In Chinese]

[11] Pollheimer J.: "The role of the invasive, placental trophoblast in human pregnancy". *Wien Med Wochenschr*, 2012, *162*, 187-190.

[12] Ietta F., Wu Y., Winter J., Xu J., Wang J., Post M., *et al.*: "Dynamic HIF1A regulation during human placental development". *Biol Reprod*, 2006, *75*, 112-121.

[13] Biberoglu E., Kirbas A., Daglar K., Biberoglu K., Timur H., Demirtas C., *et al.*: "Serum angiogenic profile in abnormal placentation". *J Matern Fetal Neonatal Med*, 2016, *29*, 3193-3197.

[14] Maebayashi A., Yamamoto T., Azuma H., Kato E., Yamamoto N., Murase T., *et al.*: "Expression of placenta growth factor, soluble fms-like tyrosine kinase-1, metal-responsive transcription factor-1, heme oxygenase 1 and hypoxia inducible factor-1α mRNAs in pre-eclampsia placenta and the effect of pre-eclampsia sera on their expression of choriocarcinoma cells". *J Obstet Gynaecol Res*, 2014, *40*, 2095-2103.

[15] Kerry M.M., S Ananth K., Stillman I.E., Peter C., Dorothy P., Thomas E.: "Does soluble fms-like tyrosine kinase-1 regulate placental invasion? Insight from the invasive placenta". *Am J Obstet Gynecol*, 2014, *210*, 68.e1-e4.

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