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ORIGINAL RESEARCH

# Maternal and Perinatal Risk Factors for Infantile Hemangioma: A Matched Case-Control Study with a Large Sample Size

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## ABSTRACT

***Introduction***: Infantile hemangioma (IH) is the most common benign tumor in infancy, but information about its pathogenesis is limited. The aim of this study was to determine maternal and perinatal risk factors for IH.

***Methods***: A total of 1033 IH patients were enrolled in the study between 2017 and 2020. IH patients were matched with controls by sex. Trained investigators collected detailed information from the participants. Logistic regression models were used for multivariate analysis.

***Results***: The statistical analysis demonstrated that miscarriage history (odds ratio [OR] = 4.275; 95% confidence interval [CI] [3.195, 5.720]), anemia in pregnancy (OR = 4.228; 95% CI [3.083, 5.799]), preterm premature rupture of membranes (PPROM) (OR = 3.182; 95% CI [1.359, 7.454]), placenta previa (OR = 2.440; 95% CI [1.787, 3.333]), threatened miscarriage (OR = 2.290; 95% CI [1.726, 3.039]), premature rupture of membranes (PROM) (OR = 1.785; $P < 0.05$), progesterone use (OR = 1.614; $P < 0.001$) and abnormal amniotic fluid volume (OR = 1.499; $P < 0.05$) were independent risk factors for IH. Gestational diabetes mellitus (GDM) (OR = 0.607; 95% CI [0.464, 0.794]), multiple gestations (OR = 0.407; 95% CI [0.232, 0.713]), hypothyroidism (OR = 0.407; 95% CI [0.227, 0.730]) and uterine fibroids (OR = 0.393; 95% CI [0.250, 0.618]) may reduce the risk of IH.

***Conclusions***: Maternal and perinatal factors are closely associated with IH occurrence. Our study provides reliable clues to guide further exploration of the pathogenesis of IH.

***Trial Registration***: ClinicalTrials.gov, NCT03331744.

***Plain Language Summary***: Infantile hemangioma is the most common benign tumor in children, which seriously affects appearance and function and even threatens life. The pathogenesis is not clear, a detailed case-control study of the maternal and perinatal periods with a large sample size will facilitate the development of individualized and precise treatment, early and timely interventions for high-risk children and improvement of prognosis. Our study found that miscarriage history,

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anemia in pregnancy, preterm premature rupture of membranes (PPROM), placenta previa, threatened miscarriage, premature rupture of membranes (PROM), progesterone use and abnormal amniotic fluid volume were independent risk factors for IH.

**Keywords:** Angiogenesis; Case–control study; Dermatology; Pediatrics; Vascular tumors

**Key Summary Points**

***Why carry out this study?***

The occurrence of infantile hemangioma is closely related to prenatal factors, and a detailed large-sample study on the risk factors for infantile hemangioma can provide a reliable basis for revealing its pathogenesis and searching for potential therapeutic targets

As a detailed, large-sample matched case-control study, our research sheds light on maternal and perinatal risk factors that can be associated with the onset of infantile hemangioma

***What was learned from this study?***

A total of 1033 cases were included; information was collected on the localizations, descriptions, morphological subtypes and complications of the hemangiomas

Miscarriage history, anemia in pregnancy, preterm premature rupture of membranes (PPROM), placenta previa, threatened miscarriage, premature rupture of membranes (PROM), progesterone use and abnormal amniotic fluid volume were independent risk factors for IH

Preterm and low birth weight (LBW) were not risk factors for IH. Gestational diabetes mellitus, multiple gestations, hypothyroidism and uterine fibroids may not predispose to IH

## INTRODUCTION

With an incidence of 4–5% [1, 2] and a female predominance [3], infantile hemangioma (IH) is the most common benign vascular tumor during childhood and is characterized by rapid proliferation and spontaneous involution. The pathogenesis of IH is complex and may be associated with both genetic and environmental factors [4, 5]. Most IHs involute spontaneously. However, in some cases, ulceration, functional deficits or even life-threatening conditions can occur [6]. Patients with these types of IHs require closer follow-up, monitoring and treatment.

Previous epidemiologic studies have found that some maternal and perinatal factors, such as female sex, prematurity, low birth weight (LBW), gestational diabetes mellitus (GDM) and progesterone use, are risk factors for IH development [2, 7, 8]. However, these findings are controversial among different studies because of the lack of comprehensive studies with large sample sizes, constraining our ability to better understand the pathogenesis of IH.

To explore the roles played by maternal and perinatal factors, we conducted a case-control study with a large sample size and analyzed the risk factors for the development of IH.

## METHODS

### Study Design and Participants

This was a case-control study conducted from October 2017 to April 2020 to assess factors associated with IH patients < 1 year old recruited from the Department of Pediatric Surgery and Department of Dermatology of West China Hospital of Sichuan University in Chengdu. Chengdu has more > 20 million residents; thus, a large sample size was ensured. Patients were diagnosed with IH by trained investigators during outpatient visits by combining clinical manifestations, physical examination, ultrasonic examinations and other methods. The control group included infants < 1 year old without IH or any congenital malformations recruited from the Department of Child Care

(every child needed to attend a clinic visit every 2 to 3 months on average before 1 year of age in China).

The criteria for inclusion were infants with at least one IH diagnosed by two investigators. The exclusion criteria were infants with any known congenital anomalies that could interfere with our judgment of the disease.

Every case with IH was matched with one control of the same sex. The study was approved by the Ethics Committee of the West China Hospital of Sichuan University. All procedures followed the study protocol and were conducted according to the Declaration of Helsinki. Written informed consent was obtained from the patient's parents or guardians before enrollment. The study was registered at www.clinicaltrials.gov (NCT03331744).

We set fixed investigators of the information collection team and conducted unified training before formally collecting patients' information. They used a standardized questionnaire designed by reviewing the literature, combining actual clinical experience and research needs to collect maternal factors (e.g., GDM and progesterone use) and perinatal factors (e.g., gestational age and birth weight) in detail. The questionnaire was administered by trained investigators.

The investigators were available to assist the completion of the questionnaires if the parents had questions on semantic or conceptual understanding. To minimize the effects of recall bias, they looked up the medical records to collect details about the mother's condition during pregnancy of every case and control. They also confirmed the data and diagnosis through laboratory, imaging examination reports and other methods. They were responsible for collecting and checking the questionnaires to ensure that there were no missing data or logical mistakes. Before starting the statistical analysis, we reviewed the results again and discarded participants with incomplete personal data.

In conclusion, although bias is inevitable, a variety of methods were adopted to minimize the bias in the operation process to ensure the accuracy of the data and research content.

## Definitions

Diseases are diagnosed with reference to guidelines and expert advice. For instance, IH was diagnosed and classified according to the definition and classification system of the International Society for the Study of Vascular Anomalies (ISSVA; www.issva.org). Anemia in pregnancy refers to maternal hemoglobin levels $< 110$ g/l in the first and third trimesters and $< 105$ g/l during the second trimester according to the World Health Organization (WHO) guidelines. Preterm was defined as gestational age $< 37$ weeks.

## Statistical Analysis

PASS 11 software was used for sample size estimation. With a 2.5% test level of each side and 85% power, at least 420 patients needed to be included. For descriptive purposes, data are presented as the means with standard deviations (SD) for continuous variables and as numbers with percentages for categorical variables. Univariable analysis was performed using the $\chi^2$ test for classified variables and the *t*-test or nonparametric test for continuous variables.

Considering the practical situation of the analysis in which many factors with a $P$ value $>$ 0.05 were still correlated with the incidence of IH to a certain extent, it was not appropriate to exclude them directly. All variables with a $P$ value $< 0.15$ in the univariable analysis were included in the subsequent logistic regression analysis to account for potential confounders and assess which variables were independently associated with IH. Before the logistic regression analysis, we performed a multicollinearity test and found no obvious linear correlation between the variables. The test level of logistic regression analysis was 0.05. The effects of the identified factors are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and $P$ values. Statistical analyses were performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA).

## DATA AVAILABILITY STATEMENT

The study was registered at www.clinicaltrials.gov (NCT03331744). Reasonable inquiries regarding our study data will be answered by the corresponding author.

## RESULTS

A total of 1033 cases and 1033 sex-matched controls were enrolled in the study after excluding 12 patients in the case group because of incomplete information. Clinical characteristics are listed in Supplementary Table S1. A total of 326 males and 707 females < 1 year old were included, and this study confirmed a female predominance in IH, as mentioned in previous studies.

Univariable analysis showed that maternal factors, including miscarriage history, ovarian cysts, anemia in pregnancy, multiple gestations, GDM, hypothyroidism, uterine fibroids, abnormal amniotic fluid volume, magnesium sulfate use, progesterone use and threatened miscarriage, and perinatal risk factors, including nuchal cord, fetal malpresentation, glucocorticoid use, preterm birth, placenta accreta, placenta previa, prolapse of umbilical cord, preterm premature rupture of membranes (PPROM) and premature rupture of membranes (PROM), were associated with IH occurrence (Tables 1 and 2). No difference was noted between cases and controls regarding funic presentation, hyperemesis gravidarum, hypertensive disorders of pregnancy, LBW, maternal alcohol consumption and maternal smoking. We performed a multicollinearity test and found no obvious linear correlation between the variables, so we included these screened risk factors in the multivariable analysis.

The multivariable analysis revealed that miscarriage history, anemia in pregnancy, PPROM, placenta previa, threatened miscarriage, PROM, progesterone use and abnormal amniotic fluid volume were risk factors for IH. IH was significantly associated with miscarriage history (odds ratio [OR] = 4.275; 95% confidence interval [CI] [3.195, 5.720]; $P < 0.001$), anemia in pregnancy (OR = 4.228; 95% CI [3.083, 5.799]; $P < 0.001$), PPROM (OR = 3.182; 95% CI [1.359, 7.454]; $P < 0.05$), placenta previa (OR = 2.440; 95% CI [1.787, 3.333]; $P < 0.001$) and threatened miscarriage (OR = 2.290; 95% CI [1.726, 3.039]; $P < 0.001$). GDM (OR = 0.607; 95% CI [0.464, 0.794]; $P < 0.001$), multiple gestations (OR = 0.407; 95% CI [0.232, 0.713]; $P < 0.05$), hypothyroidism (OR = 0.407; 95% CI [0.227, 0.730]; $P < 0.05$) and uterine fibroids (OR = 0.393; 95% CI [0.250, 0.618]; $P < 0.001$) did not predispose patients to IH (Table 3 and Fig. 1). LBW ($P = 0.343$) and preterm birth ($P = 0.414$) were not risk factors for IH.

## DISCUSSION

This case-control study was conducted in a large sample and collected detailed information about maternal and perinatal factors to provide reliable information. The results of this study identified risk factors for IH. In previous studies, different risk factors have been revealed to be related to IH, such as female sex, LBW, preterm birth, multiple gestations, GDM, placental anomalies, early-onset preeclampsia and progesterone use [2, 9–11]. However, these studies were limited by their small sample sizes, which create an inherent risk of bias. In addition, some of these factors were controversial among studies. To date, few studies on risk factors for IH, especially maternal and perinatal factors, including > 1000 patients, have been performed.

The female predominance in our study was consistent with previous results in the literature [12]. To eliminate the obvious bias caused by sex, we matched our patients with controls of the same sex. In addition, our data confirmed several risk factors that have been reported by previous studies, such as placenta previa, threatened miscarriage and progesterone use [3, 10, 13].

In brief, the nature of many risk factors (e.g., anemia) below can be attributed to the hypoxia theory [14]. Hypoxia is a common feature of numerous diseases, especially malignant tumors, which cause abnormal cell proliferation and angiogenesis [15, 16]. In this process, the

**Table 1** Selected characteristics of the study group

| | With IH ($n$ = 1033) | | Without IH ($n$ = 1033) | |
|---|---|---|---|---|
| | $n$ | % | $n$ | % |
| Maternal factors | | | | |
| Maternal smoking | 25 | 2.42 | 18 | 1.74 |
| Maternal alcohol consumption | 45 | 4.36 | 36 | 3.48 |
| Miscarriage history | 305 | 29.53 | 83 | 8.03 |
| Ovarian cysts | 34 | 3.29 | 48 | 4.65 |
| Uterine fibroids | 38 | 3.68 | 93 | 9.00 |
| Perinatal factors | | | | |
| Hypertensive disorders of pregnancy | 37 | 3.58 | 31 | 3.00 |
| GDM | 134 | 12.97 | 221 | 21.39 |
| Anemia in pregnancy | 263 | 25.46 | 63 | 6.10 |
| Hypothyroidism in pregnancy | 96 | 9.29 | 189 | 18.30 |
| Hyperemesis gravidarum | 37 | 3.58 | 38 | 3.68 |
| Multiple gestations | 34 | 3.29 | 51 | 4.94 |
| Fetal malpresentation | 124 | 12.00 | 91 | 8.81 |
| Placenta previa | 227 | 21.97 | 81 | 7.84 |
| Placenta accreta | 9 | 0.87 | 1 | 0.10 |
| PROM | 136 | 13.17 | 82 | 7.94 |
| PPROM | 40 | 3.87 | 11 | 1.06 |
| Abnormal amniotic fluid volume | 142 | 13.75 | 99 | 9.58 |
| Nuchal cord | 517 | 50.05 | 432 | 41.82 |
| Prolapse of umbilical cord | 5 | 0.48 | 0 | 0 |
| Funic presentation | 1 | 0.10 | 0 | 0 |
| Threatened miscarriage | 271 | 26.23 | 110 | 10.65 |
| Fetal distress | 79 | 7.65 | 45 | 4.36 |
| Medication | | | | |
| Progesterone | 339 | 32.82 | 187 | 18.10 |
| Euthyrox | 77 | 7.45 | 149 | 14.42 |
| Glucocorticoids | 58 | 5.61 | 33 | 3.19 |
| Magnesium sulfate | 0 | 0 | 19 | 1.84 |
| Preterm | 123 | 11.91 | 93 | 9.00 |
| LBW | 78 | 7.55 | 67 | 6.49 |

GDM, gestational diabetes mellitus; PROM, premature rupture of membrane; PPROM, preterm premature rupture of membranes; LBW, low birth weight

**Table 2** Univariable analysis of risk factors for IH

| Variable | $\chi^2$ | Odds Ratio (95% Confidence Interval) | *P value* |
|---|---|---|---|
| Placenta accreta | 6.431 | 9.071 (1.147, 71.722) | 0.011 |
| Anemia in pregnancy | 145.688 | 5.259 (3.932, 7.033) | 0.000 |
| Miscarriage history | 156.391 | 4.795 (3.693, 6.226) | 0.000 |
| PPROM | 16.908 | 3.743 (1.909, 7.336) | 0.000 |
| Placenta previa | 81.333 | 3.310 (2.526, 4.338) | 0.000 |
| Threatened miscarriage | 83.418 | 2.984 (2.344, 3.799) | 0.000 |
| Progesterone use | 58.927 | 2.210 (1.801, 2.712) | 0.000 |
| Fetal distress | 9.918 | 1.818 (1.247, 2.650) | 0.002 |
| Glucocorticoids | 7.185 | 1.803 (1.165, 2.789) | 0.007 |
| PROM | 14.954 | 1.758 (1.317, 2.347) | 0.000 |
| Abnormal amniotic fluid volume | 8.685 | 1.504 (1.145, 1.975) | 0.003 |
| Fetal malpresentation | 5.653 | 1.412 (1.061, 1.879) | 0.017 |
| Maternal smoking | 1.164 | 1.399 (0.758, 2.579) | 0.281 |
| Nuchal cord | 14.081 | 1.394 (1.172, 1.658) | 0.000 |
| Preterm | 4.653 | 1.366 (1.028, 1.815) | 0.031 |
| Maternal alcohol consumption | 1.041 | 1.261 (0.807, 1.972) | 0.308 |
| Hypertensive disorders of pregnancy | 0.547 | 1.201 (0.739, 1.951) | 0.459 |
| LBW | 0.897 | 1.178 (0.839, 1.652) | 0.343 |
| Hyperemesis gravidarum | 0.014 | 0.973 (0.613, 1.543) | 0.906 |
| Ovarian cysts | 2.489 | 0.698 (0.446, 1.093) | 0.115 |
| Multiple gestations | 3.546 | 0.655 (0.421, 1.020) | 0.060 |
| GDM | 25.745 | 0.548 (0.433, 0.692) | 0.000 |
| Prolapse of umbilical cord | 5.012 | 0.499 (0.478, 0.521) | 0.025 |
| Magnesium sulfate | 19.176 | 0.495 (0.474, 0.517) | 0.000 |
| Euthyrox | 25.755 | 0.478 (0.358, 0.639) | 0.000 |
| Hypothyroidism in pregnancy | 35.204 | 0.458 (0.352, 0.595) | 0.000 |
| Uterine fibroids | 24.655 | 0.386 (0.262, 0.569) | 0.000 |
| Funic presentation | - | - | 0.500 |

GDM, gestational diabetes mellitus; LBW, low birth weight; PPROM, preterm premature rupture of membranes; PROM, premature rupture of membrane

-Fisher's exact examination was used for analysis

Factors reported in gray were excluded by univariable analysis

increased expression of hypoxia inducible factor-1α (HIF-1α) plays a central role in cellular mechanisms triggered in response to hypoxia [17]. Exposure to hypoxic environments in early life produces more HIF-1α, which contributes to the remodeling of the vasculature into a branched vascular tree to meet increased oxygen and nutrient requirements.

Our results unprecedentedly identified anemia in pregnancy as an important independent risk factor for IH, a point that previous studies have never assessed. In fact, anemia is a common condition in pregnancy, and its etiology varies. In one Brazilian study, > 80% of pregnant women reported using iron supplementation; however, more than half of these women had become anemic [18].

Anemia in pregnancy is commonly related to a decrease in hemoglobin, making the fetus more susceptible to hypoxia. Higher rates of maternal and perinatal morbidities, such as preeclampsia, placenta previa, preterm birth and LBW, have been demonstrated to be related to this condition [13, 19, 20]. Expectedly, iron deficiency anemia in pregnant rats presented a significant increase in HIF-1α compared to the controls [21].

This study found a close correlation between miscarriage history and IH, which has been neglected in many studies. Although

**Table 3** Multivariable logistic regression analysis of risk factors for IH

| Risk factors | β | *Walds* | *P* values | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | LL | UL |
| Miscarriage history | 1.453 | 95.602 | 0.000 | 4.275 | 3.195 | 5.720 |
| Anemia in pregnancy | 1.442 | 80.032 | 0.000 | 4.228 | 3.083 | 5.799 |
| Placenta accreta | 1.385 | 1.628 | 0.202 | 3.996 | 0.476 | 33.564 |
| PPROM | 1.158 | 7.106 | 0.008 | 3.182 | 1.359 | 7.454 |
| Placenta previa | 0.892 | 31.451 | 0.000 | 2.440 | 1.787 | 3.333 |
| Threatened miscarriage | 0.829 | 32.981 | 0.000 | 2.290 | 1.726 | 3.039 |
| PROM | 0.580 | 11.593 | 0.001 | 1.785 | 1.279 | 2.492 |
| Progesterone use | 0.479 | 15.432 | 0.000 | 1.614 | 1.271 | 2.050 |
| Fetal distress | 0.440 | 3.797 | 0.051 | 1.553 | 0.997 | 2.418 |
| Abnormal amniotic fluid volume | 0.405 | 6.247 | 0.012 | 1.499 | 1.091 | 2.060 |
| Euthyrox | 0.227 | 0.485 | 0.486 | 1.255 | 0.663 | 2.376 |
| Preterm | 0.164 | 0.668 | 0.414 | 1.178 | 0.795 | 1.745 |
| Glucocorticoids | 0.159 | 0.316 | 0.574 | 1.172 | 0.674 | 2.038 |
| Fetal malpresentation | 0.096 | 0.311 | 0.577 | 1.101 | 0.785 | 1.543 |
| Nuchal cord | 0.083 | 0.613 | 0.434 | 1.087 | 0.882 | 1.338 |
| Ovarian cysts | -0.452 | 2.848 | 0.092 | 0.636 | 0.376 | 1.076 |
| GDM | -0.500 | 13.278 | 0.000 | 0.607 | 0.464 | 0.794 |
| Multiple gestations | -0.899 | 9.871 | 0.002 | 0.407 | 0.232 | 0.713 |
| Hypothyroidism in pregnancy | -0.900 | 9.098 | 0.003 | 0.407 | 0.227 | 0.730 |
| Uterine fibroids | -0.934 | 16.320 | 0.000 | 0.393 | 0.250 | 0.618 |
| Prolapse of umbilical cord | 21.204 | 0.000 | 0.999 | † | 0.000 | - |
| Magnesium sulfate | -21.574 | 0.000 | 0.998 | † | 0.000 | - |

GDM, gestational diabetes mellitus; PROM, premature rupture of membrane; PPROM, preterm premature rupture of membranes

†There were few related cases, and no results were obtained after 20 cycles

Factors reported in yellow are risk factors, and those reported in green are protective factors

miscarriage occurs because of many causes, such as parental chromosomal rearrangements and uterine defects, damage to the uterus and endometrium caused by miscarriage should not be ignored [22–24]. During placental development, some aspects of angiogenesis precede the generation of the vasculature and lead to remodeling of the vascular plexus into a branched vascular tree to ensure increased nutritional and gas exchange. Increased expression of HIF-1α in the peri-implantation endometrium in women with recurrent miscarriage has been found [25].

For decades, preterm birth and LBW have been considered risk factors for IH worldwide [11, 26]; however, with a limited sample size and incomplete risk factors, most of the recent studies on this topic have focused on non-Asians. Studies on large samples of Asians are more limited. In the present study, we did not identify preterm birth and LBW as independent risk factors. A case-control study in China did not list preterm birth and LBW as risk factors, and most recently, a study from Japan did not list preterm birth and LBW as risk factors, which is partly due to racial and ethnic differences [12, 27]. Asian women have also been demonstrated to be less likely to have LBW babies [28].

Most of the literature tends to relate preterm birth and LBW to the hypoxia theory [11, 26, 29]. However, preterm birth and LBW can be associated with many factors, such as race, pregnancy history, older maternal age and assisted reproductive technology [30]. With advances in medical technology, doctors have taken measures to promote fetal development

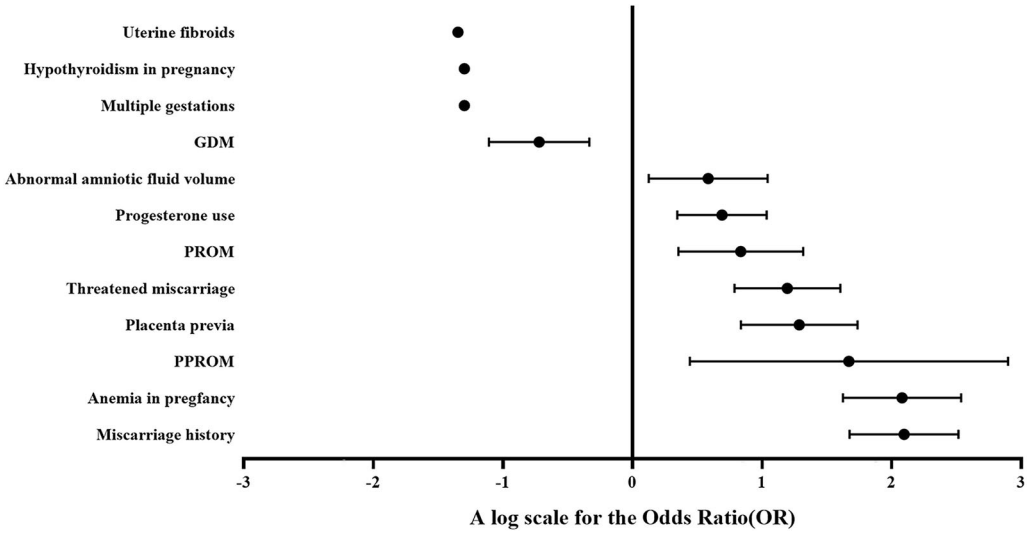


**Fig. 1** Risk factors for infantile hemangioma. A log scale for the odds ratio (OR) was used to ensure that the X-axis was symmetric. The OR and 95% confidence interval (CI) of every factor are displayed. $X = 0$ in the figure represents OR = 1. When OR = 1 is included in the 95% CI, the results are nonsignificant. Factors whose ORs are $< 1$ are considered factors not predisposing to infantile hemangioma (IH), and those whose ORs are $> 1$ are considered risk factors. *PPROM* preterm premature rupture of membranes; *PROM* premature rupture of membrane; *GDM* gestational diabetes mellitus

and to appropriately delay the birth of preterm infants. In addition, doctors also provide infants with effective care after birth. Together, these measures may reduce preterm infants' risk of suffering hypoxia.

Quite a few reports have shown that GDM is associated with IH because GDM can impair placental functions (e.g., villous immaturity) [31, 32]. GDM is a condition in which the placenta can maintain its function to protect an infant from chronic hypoxemia [31, 33]. Vascular endothelial growth factor receptor (VEGFR) is believed to play an important role in the pathogenesis of IH, but reduced VEGFR-1 and VEGFR-2 levels were found in placentas from women with GDM [34, 35]. Therefore, we cannot simply jump to the conclusion that GDM can impair placental function and serve as a risk factor for IH.

Previous studies considered multiple gestations as a risk factor for IH because multiple gestations are more likely to lead to preterm birth and LBW [12]. However, in our study, we did not identify multiple gestations as an independent risk factor. In a practical situation, mothers with multiple gestations may be examined more thoroughly and receive medical treatment immediately [36]. Moreover, to control the bias and ensure accuracy as much as possible, we implemented numerous measures, such as a large sample size, patients matched by sex, more variables included and medical records queries when necessary. Therefore, our study can better reflect current obstetrical care and reveal the real risk factors for IH. Overall, we were not surprised by our conclusion to which the data led.

Our study did not identify hypothyroidism or uterine fibroids as a risk factor. Thyroid hormone is important in the invasive function of extravillous trophoblasts [37]. The levels of thyroid hormone or thyroid-stimulating hormone (TSH) can influence the development of preeclampsia [38]. Supplementation with thyroid hormone may reduce TSH levels, helping the placenta maintain normal function. One pathogenic etiology of uterine fibroids is estrogen, a hormone that is also important in IH pathogenesis [39]. Estrogen may be produced locally via aromatase activity in fibroid cells.

Exposure to estrogen may occur through local production rather than via the placenta [39], so increased estrogen may not exert the pathogenic effects of IH through the placenta.

In addition to conforming to previously identified risk factors for IH, we also identified an association between maternal and perinatal factors and IH. Higher quality studies conducted in multiple centers are necessary for further exploration, which may provide more reliable and valuable insights into the pathogenesis of IH.

### Limitations

Although our study provides unique insights into the pathogenesis of IH, our study had some limitations. This was a case-control study with a large sample size, but we were not able to further investigate the period and severity of the events in pregnancy. In addition, confounding and recall bias are inevitable, and the study design may limit the generalizability of our results to other centers and may introduce referral bias because the patients included in our study were from a tertiary referral center.

## CONCLUSIONS

In summary, the pathogenesis of IH is strongly associated with maternal and perinatal factors. As a case-control study with a large sample size, our study identified miscarriage history, anemia in pregnancy, PPROM, placenta previa, threatened miscarriage, PROM, progesterone use and abnormal amniotic fluid volume as risk factors for IH. We did not identify preterm birth or LBW as risk factors for IH. We also revealed that GDM, multiple gestations, hypothyroidism and uterine fibroids did not predispose patients to IH.

In brief, our results provide a reliable basis for the study of the pathogenesis and treatment of IH. Children with these risk factors should be monitored and followed up more closely in the clinic for early detection and intervention decisions to improve outcomes.

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***Authorship.*** All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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***Disclosures.*** Xue Gong, Tong Qiu, Liwei Feng, Kaiying Yang, Shiyi Dai, Jiangyuan Zhou, Xuepeng Zhang, Siyuan Chen and Yi Ji have nothing to disclose.

***Compliance with Ethics Guidelines.*** The study was approved by the Ethics Committee of the West China Hospital of Sichuan University. The ethics committee reference number of this

study was 2017 (414). All procedures followed the study protocol and were conducted according to the Declaration of Helsinki. Written informed consent was obtained from the patient's parents or guardians before enrollment.

***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Prior Presentation.*** Portions of this research are planned to be presented at the 2022 International Society for the Study of Vascular Anomalies (ISSVA) World Congress.



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