

# Analysis of the anemia characteristics in early pregnancy and outcomes of pregnant women with hemoglobin H disease

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**Abstract. – OBJECTIVE:** This study aimed to analyze the anemia characteristics in early pregnancy of pregnant women with hemoglobin H (Hb H) disease and their pregnancy outcomes, and to provide reference to the pregnancy management and treatment of these women.

**PATIENTS AND METHODS:** Twenty-eight cases of pregnant women who had been diagnosed with Hb H disease in the Second Affiliated Hospital of Guangxi Medical University from August 2018 to March 2022 were retrospectively analyzed. Moreover, 28 cases of normal pregnant women in the same period were randomly enrolled as a control group for comparison. The means and percentages of the anemia characteristics in early pregnancy and the pregnancy outcomes were calculated and the analysis of variance, Chi-square test, and Fisher's exact test were applied for comparison.

**RESULTS:** A total of 13 cases of missing type (46.43%) and 15 cases of non-missing type (53.57%) were observed in the 28 cases of pregnant women with Hb H disease. The genotypes were as follows: 8 cases of  $-\alpha^{3.7}/--^{SEA}$  (28.57%), 4 cases of  $-\alpha^{4.2}/--^{SEA}$  (14.29%), 1 case of  $-\alpha^{4.2}/--^{THAI}$  (3.57%), 9 cases of  $\alpha^{CS}\alpha/--^{SEA}$  (32.14%), 5 cases of  $\alpha^{WS}\alpha/--^{SEA}$  (17.86%), and 1 case of  $\alpha^{QS}\alpha/--^{SEA}$  (3.57%). Twenty-seven patients with Hb H disease (96.43%) were anemic, including 5 cases of mild anemia (17.86%), 18 cases of moderate anemia (64.28%), 4 cases of severe anemia (14.29%), and 1 case of non-anemia (3.57%). Compared with the control group, the Hb H group had significantly higher red blood cell count and significantly lower Hb, mean corpuscular volume, and mean corpuscular hemoglobin, and the differences were statistically significant ( $p < 0.05$ ). The Hb H group had higher incidence rates of blood transfusion during pregnancy (BTDP), oligohydramnios fetal growth restrictions (FGR), and fetal distress than the control group. The weights of neonates were lower in the Hb H group than in the control group. Statistically significant dif-

ferences were found between these two groups ( $p < 0.05$ ).

**CONCLUSIONS:** The genotype missing type of pregnant women with Hb H disease was mainly  $-\alpha^{3.7}/--^{SEA}$  and the non-missing type was mainly  $\alpha^{CS}\alpha/--^{SEA}$ . Hb H disease can easily cause various degrees of anemia (mainly moderate anemia in this study). Moreover, it can increase the incidence rate of pregnancy complications such as BTDP, oligohydramnios, FGR, and fetal distress, which will reduce the weight of neonates and seriously affect maternal and infant safety. Therefore, maternal anemia and fetal growth and development should be monitored during pregnancy and delivery, and transfusion therapy should be used to improve adverse pregnancy outcomes caused by anemia when necessary.

*Key Words:*

Hemoglobin h disease,  $\alpha$ -thalassemia, Early pregnancy, Anemia, Pregnancy outcomes.

## Introduction

$\alpha$ -Thalassemia is a type of hemolytic anemia caused by the insufficient synthesis of  $\alpha$ -globin peptide chains, which is a common autosomal recessive disorder resulting from  $\alpha$ -globin gene deletion or point mutation. The prevalence of  $\alpha$ -thalassemia is up to 30%<sup>1,2</sup>. Hemoglobin H (Hb H) disease is an intermediate type of  $\alpha$ -thalassemia caused by the significant reduction of  $\alpha$ -globin peptide chains and formation of tetramers by excessive globin chains, which are caused by three  $\alpha$ -globin gene deletions or point mutations. Although Hb H is less common than  $\alpha$ -light thalassemia, it is one of the most serious types of  $\alpha$ -thalassemia, including missing type ( $-\alpha^{3.7}/--^{SEA}$

and  $-\alpha^{4.2}/-^{SEA}$ ), non-missing type ( $\alpha^{WS}\alpha/-^{SEA}$ ,  $\alpha^{CS}\alpha/-^{SEA}$ , and  $\alpha^{QS}\alpha/-^{SEA}$ ), and  $\alpha$ -non-deletion Hb H disease of homozygotes for globin gene mutations such as  $\alpha^{CS}\alpha/\alpha^{CS}\alpha$  and  $\alpha^{QS}\alpha/\alpha^{QS}\alpha$ <sup>3,4</sup>. In China, Guangxi Province has the highest incidence of thalassemia; about 20%-25% of the population carry the thalassemia gene<sup>5</sup>, of which the incidence of Hb H disease is about 0.43%, and about 200,000 patients suffer from Hb H disease<sup>6</sup>. Many female patients with Hb H disease face fertility problems. The clinical manifestations of Hb H vary in severity, ranging from mild or no anemia to severe thalassemia. Severe anemia can lead to adverse outcomes for pregnant women and fetuses. Currently, there are only few studies<sup>6</sup> on the effect of Hb H disease on maternal and infant outcomes. In this study, the clinical data of 28 cases of pregnant women complicated with Hb H disease in the Second Affiliated Hospital of Guangxi Medical University were investigated. This study aimed to analyze the anemia characteristics in early pregnancy of pregnant women with Hb H disease and their pregnancy outcomes, and to provide reference to the pregnancy management and treatment of these women.

## Patients and Methods

### General Materials

Twenty-eight cases of pregnant women who had been diagnosed with Hb H disease (Hb H group) in the Second Affiliated Hospital of Guangxi Medical University from August 2018 to March 2022 were retrospectively analyzed. Moreover, 28 cases of normal pregnant women in the same period were enrolled as a control group for comparison. The age of patients in the Hb H group ranged from 19 years to 40 years, with an average age of  $(30.07 \pm 5.54)$  years. The Hb H group had an average pregnancy time of  $(2.07 \pm 1.05)$  times, average delivery time of  $(1.43 \pm 0.57)$  times, and average body mass index (BMI) of  $(20.54 \pm 2.81)$ . The age of patients in the control group ranged from 19 years to 40 years, with an average age of  $(29.21 \pm 4.07)$  years. The control group had an average pregnancy time of  $(2.04 \pm 0.92)$  times, average delivery time of  $(1.43 \pm 0.57)$  times, and average BMI of  $(21.25 \pm 2.56)$ . There was no statistical difference among age, pregnancy and delivery times, and BMI of the two groups ( $p > 0.05$ ). This study was approved by the medical ethics committee of the Second Affiliated Hospital of Guangxi Medical University, and all patients have signed informed consent.

### Methods and Indicators

#### Hematological index

In the early stage of pregnancy (the first 14 weeks of pregnancy), patients' blood was drawn to detect their red blood cell (RBC) count, Hb, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH). *Pregnancy outcomes*

Pregnancy outcomes included the degree of anemia, history of blood transfusion during pregnancy (BTDP), oligohydramnios, fetal growth restrictions (FGR), fetal distress, cesarean section (CS) rate, postpartum hemorrhage, neonatal asphyxia, neonatal weight, and low birth weight.

#### Diagnostic Criteria

##### Anemia during pregnancy<sup>7</sup>

Anemia during pregnancy was defined as Hb concentration in early pregnancy lower than 110 g/L and classified as follows: mild anemia ( $100 \text{ g/L} \leq \text{Hb} < 110 \text{ g/L}$ ), moderate anemia ( $70 \text{ g/L} \leq \text{Hb} < 100 \text{ g/L}$ ), and severe anemia ( $\text{Hb} < 70 \text{ g/L}$ ).

##### FGR<sup>8</sup>

FGR was defined as a fetus with an estimated fetal weight or abdominal circumference smaller than 10% of the body weight of the pregnant woman.

##### Asphyxia neonatorum

Neonates whose Apgar scores at 1 min after birth are lower than 7 were defined as asphyxia neonatorum.

#### Statistical Analysis

Data were analyzed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA). The homoscedastic measurements that conform to the normal distribution were described by mean  $\pm$  standard deviation, and variance analysis was adopted to compare three groups of data. The least significant difference test was used for pairwise comparison. Enumeration data were expressed as frequency or rate and tested by Chi-square test. When the sample size is less than 40, the theoretical frequency is less than 5, and Fisher's exact test was adopted. Differences were considered statistically significant with  $p$ -values less than 0.05.

## Results

### Genotype Composition of Hb H Disease and Distribution of Anemia Degree

A total of 13 cases of missing type (46.43%) and 15 cases of non-missing type (53.57%) were found in the Hb H group. The genotypes were as fol-

**Table I.** Genotype composition of Hb H disease and distribution of anemia degree [n (%)].

Type of Hb H Disease	Genotype	n (%)	No Anemia (n)	Mild Anemia (n)	Moderate Anemia (n)	Severe Anemia (n)
Missing Type	- $\alpha^{3.7}/\text{--}_{\text{SEA}}$	8 (28.57)	0 (0.00)	1 (3.57)	7 (25.00)	0 (0.00)
	- $\alpha^{4.2}/\text{--}_{\text{SEA}}$	4 (14.29)	0 (0.00)	0 (0.00)	3 (10.71)	1 (3.57)
	- $\alpha^{4.2}/\text{--}_{\text{THAI}}$	1 (3.57)	0 (0.00)	0 (0.00)	1 (3.57)	0 (0.00)
Non-missing Type	$\alpha^{\text{CS}}\alpha/\text{--}_{\text{SEA}}$	9 (32.14)	0 (0.00)	0 (0.00)	6 (21.43)	3 (10.71)
	$\alpha^{\text{WS}}\alpha/\text{--}_{\text{SEA}}$	5 (17.86)	1 (3.57)	4 (14.29)	0 (0.00)	0 (0.00)
	$\alpha^{\text{QS}}\alpha/\text{--}_{\text{SEA}}$	1 (3.57)	0 (0.00)	0 (0.00)	1 (3.57)	0 (0.00)
Total		28 (100.00)	1 (3.57)	5 (17.86)	18 (64.28)	4 (14.29)

lows: 8 cases of  $-\alpha^{3.7}/\text{--}_{\text{SEA}}$  (28.57%), 4 cases of  $-\alpha^{4.2}/\text{--}_{\text{SEA}}$  (14.29%), 1 case of  $-\alpha^{4.2}/\text{--}_{\text{THAI}}$  (3.57%), 9 cases of  $\alpha^{\text{CS}}\alpha/\text{--}_{\text{SEA}}$  (32.14%), 5 cases of  $\alpha^{\text{WS}}\alpha/\text{--}_{\text{SEA}}$  (17.86%), and 1 case of  $\alpha^{\text{QS}}\alpha/\text{--}_{\text{SEA}}$  (3.57%). Twenty-seven patients with Hb H disease (96.43%) were anemic, including 5 cases of mild anemia (17.86%), 18 cases of moderate anemia (64.28%), 4 cases of severe anemia (14.29%), and 1 case of non-anemia (3.57%) (Table I).

### Comparison of the Hematological Index in Early Pregnancy

Compared with the control group, the Hb H group had significantly higher RBC count and significantly lower Hb, MCV, and MCH, and the differences were statistically significant ( $p < 0.05$ ) (Table II).

### Comparison of Pregnancy Outcomes

The incidence rates of BTDP, oligohydramnios, FGR, and fetal distress were all higher in the Hb

H group than in the control group. The weights of neonates in the Hb H group were lower than those in the control group. Statistically significant differences were found between these two groups ( $p < 0.05$ ). There was no significant difference in the CS and postpartum hemorrhage rates between the two groups ( $p > 0.05$ ) (Table III).

## Discussion

### Genotype Composition of Hb H Disease in Pregnancy

As a common single-gene genetic disease in southern China,  $\alpha$ -thalassemia is a kind of hemolytic anemia caused by the synthetic disorders of  $\alpha$ -globin peptide chains. Hb H disease is caused by the deletion of three  $\alpha$ -globin genes (missing type) or two  $\alpha$ -globin genes combined with one non-deletion gene mutation (non-missing type), resulting in only one functional  $\alpha$ -globin gene ex-

**Table II.** Comparison of the hematological index in early pregnancy between the two groups.

Group	n (%)	RBC ( $\times 10^{12}/\text{L}$ )	Hb (g/L)	MCV (fL)	MCH (pg)
Hb H Group	28	4.47 $\pm$ 0.80	88.03 $\pm$ 13.26	66.97 $\pm$ 9.11	20.06 $\pm$ 2.35
	28	4.11 $\pm$ 0.34	122.77 $\pm$ 7.24	87.91 $\pm$ 5.71	30.00 $\pm$ 2.41
<i>p</i>		0.032	<0.001	<0.001	<0.001

**Table III.** Comparison of the pregnancy outcomes of the two groups.

Groups	n (%)	BTDP	Oligohydramnios	FGR	FD	CS	PPH	WN (g)	NA
Hb H Group	28	4 (14.29)	9 (32.14)	6 (21.43)	7 (25.00)	10 (35.71)	1 (3.57)	2,949.29 $\pm$ 471.04	1 (3.57)
Control Group	28	0 (0.00)	1 (3.57)	1 (3.57)	1 (3.57)	8 (28.57)	1 (3.57)	3,320.89 $\pm$ 470.49	0 (0.00)
<i>p</i>		0.038	0.005	0.043	0.022	0.567	1.000	0.005	0.313

BTDP: blood transfusion during pregnancy; FGR: fetal growth restrictions; FD: fetal distress; CS: cesarean section; PPH: postpartum hemorrhage rate; WN: weights of neonates (g); NA: neonatal asphyxia.

istence. Hb H disease is a highly heterogeneous disease with significant geographical and ethnic differences. The main genotypes of Hb H disease in Iran are  $-\text{MED}/-\alpha^{3.7}$  and  $-\text{20.5}/\alpha^{-5\text{nt}}\alpha$ , those in California and Ontario are  $-\alpha^{3.7}/-\text{SEA}$  and  $-\text{FIL}/-\alpha^{3.7}$ , and that in Thailand is  $\alpha^{\text{CS}}\alpha/-\text{SEA}^{9-11}$ . In Guangxi, the main genotypes of missing type and non-missing type Hb H disease are  $-\alpha^{3.7}/-\text{SEA}$  and  $\alpha^{\text{CS}}\alpha/-\text{SEA}$ , respectively<sup>12</sup>. In this study, there are 13 cases of missing type (46.43%) and 15 cases of non-missing type (53.57%). The main genotype of the missing type is  $-\alpha^{3.7}/-\text{SEA}$  (28.57%), and that of the non-missing type is  $\alpha^{\text{CS}}\alpha/-\text{SEA}$  (32.14%), which is consistent with previous reports.

### **Anemia and Hematological Indexes in Early Pregnancy of Pregnant Women with Hb H Disease**

With various degrees of anemia, the clinical manifestations of patients with Hb H disease are highly heterogeneous. Turkey's research center has reported<sup>13</sup> that the average Hb of patients with Hb H disease is 87 g/L and that the Hb level of patients with Hb H deletion is generally higher than that of patients without Hb H deletion. Among patients with  $\alpha^{\text{CS}}\alpha/-\text{SEA}$  genotype, the proportion of moderate and severe anemia is the highest, followed by that of patients with  $\alpha^{\text{QS}}\alpha/-\text{SEA}$  genotype<sup>14</sup>. With a total of 18 cases (64.28%), the Hb level of pregnant women with Hb H diseases in this study is  $(88.03 \pm 13.26)$  g/L, showing moderate anemia. The most severe genotype is  $\alpha^{\text{CS}}\alpha/-\text{SEA}$ . Among the nine cases of patients with this genotype, six cases had moderate anemia (21.43%), and three cases had severe anemia (10.71%). Patients with Hb H have had moderate to severe anemia in early pregnancy, and the rise of blood volume during pregnancy would aggravate anemia, leading to long-term chronic hypoxia and increasing the incidence of adverse pregnancy outcomes. This study also found that the Hb H group had significantly lower MCV and MCH and higher RBC count than the control group. Long-term anemia has been considered to promote the bone marrow to produce more red cells, and Hb H would cause damage to red cells, destroy the regulatory effect of the red cell membrane on RBCs, increase the volume of red cells and fragility of the cell membrane, decrease the deformation ability, and then cause hemolysis. As a result, the body would produce many RBC fragments, and the RBC value would increase. MCV and MCH could be regarded as important indicators for Hb H disease screening<sup>15</sup>.

### **Effects of Hb H Disease on Pregnancy Outcome**

Anemia during pregnancy increases complications such as gestational diabetes mellitus, polyhydramnios, postpartum hemorrhage, premature birth, low birth weight, neonatal complications, and neonatal intensive care unit admission<sup>16</sup>. Patients with Hb H have a high-risk pregnancy. During pregnancy, their blood volume increases with hemodilution, and their anemia becomes more serious. The oxygen-carrying capacity of pregnant women with Hb H diseases decreases, which would increase the probability of BTDP. In this study, pregnant women with Hb H disease mainly had moderate anemia; however, there were four cases of severe anemia, which is significantly more than that of the control group, and they required blood transfusion. In addition, moderate and severe anemia would cause hypoxia of the placenta or uterine decidua and functional decline of placental circulation. As a result, the supply of oxygen and nutrients to the fetus would be insufficient. Some studies<sup>17</sup> have shown that Hb H disease leads to a significant increase in the incidence of premature birth, FGR, and low birth weight and significantly increases the risk of adverse fetal outcomes. Hb H disease is also a hereditary disease, which increases the incidence of  $\alpha$ -thalassemia and even severe  $\alpha$ -thalassemia in the offspring. In this study, the incidence rates of BTDP, oligohydramnios, FGR, and fetal distress were all higher in the Hb H group than in the control group. The weights of neonates in the Hb H group were lower than those in the control group. This study suggests that Hb H disease would significantly increase the risk of complications during pregnancy (e.g., oligohydramnios, FGR, and fetal distress), affect the normal growth of the fetus, reduce the weights of neonates, and seriously affect maternal and infant health. Therefore, anemia should be corrected in time according to the severity of anemia of patients with Hb H disease during their pregnancy to reduce the occurrence of maternal and infant complications. At present, there is a controversy over whether anemia increases the CS rate, because anemia is not an indication of CS. However, anemia increases the incidence of complications during pregnancy, which may increase the incidence of CS and postpartum hemorrhage. In this study, there is no statistical significance on the rates of CS and postpartum hemorrhage, which may be affected by the number of samples.

## Conclusions

The genotypes of pregnant women with Hb H disease are still consistent with those of previous reports<sup>9-11</sup>. The deletion type is mainly  $-\alpha^{3.7}/-^{\text{SEA}}$ , and the non-deletion type is mainly  $\alpha^{\text{CS}}\alpha/-^{\text{SEA}}$ . Hb H disease can easily cause various degrees of anemia during pregnancy (mainly moderate anemia in this study). The  $\alpha^{\text{CS}}\alpha/-^{\text{SEA}}$  genotype caused the most serious anemia. Hb H disease significantly increased the risk of complications during pregnancy (e.g., oligohydramnios, FGR, and fetal distress), reduce the weight of neonates, and seriously affect maternal and infant health. During pregnancy, close attention should be paid to the maternal and infant conditions of pregnant women with Hb H disease, and if necessary, blood transfusion is required to improve the adverse pregnancy outcomes of pregnant women with Hb H disease.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

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## Ethics Approval

This study was approved by the medical Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University.

## Informed Consent

All patients have signed informed consent.

## Authors' Contributions

Junyou Su and Chen Yan contributed to the conception and design of the study; Hongfei Chen and Junru Tong contributed to the acquisition of data; Yanni Wei contributed to the analysis of data; Lingling Huang drafted the article; Li Deng made critical revisions related to relevant intellectual content of the manuscript.

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## Data Availability Statement

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

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