Analysis of the pregnancy status and outcomes of pregnant women with α-thalassemia: A retrospective clinical study

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Research Article

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Abstract

**Background:** The prevalence of α-thalassemia is high in Guangxi, and its co-occurrence with pregnancy may impede maternal system functions, with a consequent adverse effect on pregnancy progression and birth outcomes. The study objective was to compare the levels of relevant laboratory parameters, pregnancy complications, and birth outcomes of different types of α-thalassemia in pregnancy and to provide guidance on effective prevention and monitoring of perinatal complications in various types of α-thalassemia in pregnancy and improve associated pregnancy outcomes.

**Methods:** The observation group comprised 1371 singleton pregnant women with α-thalassemia. The control group comprised 680 non-thalassemia singleton pregnancies during the same period. The thalassemia genotypes of the observation group were tallied and categorized based on their respective genotypes within the group. All relevant clinical data were compared within and between groups.

**Results:** (1) The ethnic distribution among the α-thalassemia pregnancies was predominantly Han and Zhuang, with the top three genotypes --SEA/αα, -α3.7/αα, and αCSa/αα. (2) The hemoglobin in the experimental group was lower than that in the control group, with the lowest hemoglobin in the intermediate group (P < 0.001), and serum ferritin trending in the opposite direction. The most significant decreases in hemoglobin and ferritin during pregnancy were observed in the intermediate group (P < 0.001). (3) The incidences of abnormal Electrocardiograph, abnormal liver function, hypertensive disorders, Gestational Diabetes Mellitus and thyroid disorders during pregnancy were higher in the observation group than in the control group (P < 0.05). (4) The incidences of preterm labor, caesarean section and postpartum hemorrhage were all higher in the observation group than in the control group (P < 0.05). (5) The delivery weight and neonatal hemoglobin in the observation group were lower than those in the control group (P < 0.05).

**Conclusions:** Pregnant women with α-thalassemia have the lowest hemoglobin levels, the highest serum ferritin levels, more complications of pregnancy and childbirth than non-thalassemic pregnancies. Pregnancy-related indicators should be monitored and corrected in a timely manner to prevent and reduce adverse pregnancy outcomes with α-thalassemia.

Background

Thalassemia is the most common clinically inherited monogenic hemolytic anemia caused by a gene mutation or deletion, and it results in the reduced or complete loss of synthesis of the globin chains of hemoglobin. This condition is inherited in an autosomal recessive or incomplete dominant fashion [1] and is characterized by hemolysis, ineffective erythropoiesis and varying degrees of microcytic hypochromic anemia [2]. Thalassemia is prevalent in Mediterranean, African and Southeast Asian populations, with marked ethnic and geographic differences. It is clinically classified as α, β, δ and δβ depending on the type of peptide chain deficiency. Of these, α and β thalassemia are the most common.

Although β-thalassemia may be the more clinically significant form, α-thalassemia is highly prevalent throughout the tropics and almost reaching fixation (a term in population genetics denoting that a mutant allele of a particular gene has become the only allele expressed in the population, namely, that it has reached a frequency of 100%) in parts of South Asia [3]. It is estimated that approximately 5% of the world's population carries the α-thalassemia variant gene [4].

In α-thalassemia, a genetic defect causes an imbalance in the composition of hemoglobin in the blood due to a lack of or insufficient synthesis of the α-globin chain of hemoglobin, resulting in a series of complications such as anemia and hemolysis. In the case of α-thalassemia in pregnancy, the hematological system of the pregnant woman is altered, and the symptoms of anemia may worsen as the pregnancy progresses, which may affect maternal organ function and disrupt the endocrine and cardiovascular systems, with adverse effects on the pregnancy course and birth outcome. Theoretically, the degree of adverse effects may vary between different types and levels of thalassemia among pregnant women. However, there are few studies on the pregnancy status and pregnancy outcomes of pregnant women with different types of α-thalassemia. Therefore, this paper presents a retrospective analysis of the pregnancy status and birth outcomes of pregnant women with different types of α-thalassemia in an attempt to investigate the adverse effects of different types of α-thalassemia on pregnant women and the differences between them so that we can enable the prevention and early detection of complications in pregnant women with α-thalassemia. The study aims to investigate the adverse effects of different types of α-thalassemia on pregnant women and the differences between them.

Methods

1. Patient data and grouping

This is a retrospective, descriptive study. Data were retrospectively collected from clinical charts. A total of 1341 eligible pregnant women with α-thalassemia were screened per the inclusion and exclusion criteria at the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region and the First Affiliated Hospital of Guangxi Medical University from January 1, 2018, to July 30, 2022, in the obstetrics department as the observation group and then grouped within the group with reference to the Expert Consensus on Management of Thalassemia in Pregnancy (2020). The patients were classified into the following groups: carrier of α-thalassemia, -α/αα, αWSa/αα; minor α-thalassemia, -αα, -α/-α, αCSa/αα, αQSa/αα; and intermediate α-thalassemia, -α/-αTα, αCSa/αQSa, αQSa/αQSa, aCSa/aCSa. Then, we selected 680 pregnant women without thalassemia during the same period to serve as the control group.
Data on hemoglobin and serum ferritin in each trimester, ECG during pregnancy, and the presence of pregnancy complications, such as hypertension, diabetes mellitus, thyroid function disorders, liver function abnormalities, were collected from each group separately, as was clinical data on delivery outcomes such as gestational week at delivery, mode of delivery, hemorrhage, 1-min Apgar score, neonatal weight and neonatal hemoglobin.

2. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) singleton pregnancy; (2) regular obstetric examination during pregnancy; (3) clinically confirmed α-thalassemia; (4) 75 g oral glucose tolerance test (OGTT) between 24 and 28 weeks of pregnancy.

The exclusion criteria were as follows: (1) multiple pregnancy; (2) other hematological disorders in the pregnant woman; (3) prepregnancy diabetes mellitus, chronic hypertension, chronic kidney disease, abnormal thyroid function and heart disease, among others; (4) other types of thalassemia; (5) severe immune system disorders; (6) fetus with severe thalassemia; or (7) recent history of blood transfusion and intravenous iron therapy.

3. Relevant diagnostic criteria

Diagnosis of alpha-thalassemia is based on the following: all pregnant women with thalassemia are diagnosed with alpha-thalassemia after genetic testing for thalassemia at a medical institution qualified for prenatal diagnosis and have a definite thalassemia genotype.

The diagnosis of pregnancy and the stages of pregnancy are clarified with reference to the 9th edition of Obstetrics and Gynecology: gestational week <14 weeks was considered the first trimester; gestational week between 14 and 27+6 was considered the second trimester; and ≥28 gestational weeks was considered the third trimester.

The diagnostic criteria for anemia in pregnancy were as follows: very severe anemia (Hb<40 g/L); severe anemia (40-69 g/L); moderate anemia (70-99 g/L); and mild anemia (100-109 g/L).

The diagnostic criteria for gestational diabetes mellitus were as follows: three blood glucose values below 5.1, 10.0 and 8.5 mmol/L before and 1 h and 2 h after consuming sugar, respectively.

Low birth weight: full-term newborn with a birth weight of less than 2500 g.

Preterm birth: delivery at more than 28 weeks and less than 37 weeks of gestation.

Postpartum hemorrhage: bleeding within 24 hours of delivery ≥ 500 ml for vaginal delivery and ≥ 1000 ml for cesarean section.

1-minute Apgar score for newborns: The Apgar score included scores for respiration, heart rate, muscle tone, skin color, and reflexes. Each score ranged from 0-2 points, with a total of 10 points.

4. Statistical methods

All data were summarized in Excel, and SPSS 25.0 software was used for statistical analysis of the data. The measurement data were tested for normality using the D'Agostino test, indicators that were normally distributed were expressed as mean ± standard deviation (± s), one-way ANOVA was used for comparison between multiple groups, chi-square was used for the LSD test, indicators that were not normally distributed are expressed as the median and interquartile range (IQR), the Kruskal-Wallis H test was used for comparisons between multiple groups, and pairwise P < 0.05 was considered to indicate a statistically significant difference.

Results

1. Distribution of ethnicity and genotype

Among the 1371 pregnant women with α-thalassemia included in the study, the Han and Zhuang ethnic groups were overrepresented, as shown in Figure 1. In the observation group, we detected 25 genotypes, of which the most common (top three) were SEA/ααα (673 cases, 49.2%), -α3.7/αα (273 cases, 20.0%), and αCS/αα (153 cases, 11.2%), and the percentages are shown in Figure 2.

2. Comparison of hemoglobin and serum ferritin

The hemoglobin of the experimental group was lower than that of the control group regardless of the gestation period. With the lowest hemoglobin in the intermediate group (P value <0.001). In contrast, serum ferritin was higher in the experimental group than in the control group in all trimesters, with the highest serum ferritin in the intermediate group (P value < 0.001). For both indicators, the decrease with gestation was also most significant in the intermediate group (p value < 0.001), as shown in Figure 3.

3. Comparison of complications during pregnancy
In the comparison of the incidences of Electrocardiograph (ECG) abnormalities, gestational diabetes, thyroid function abnormalities, hypertensive disorders of pregnancy, and liver function abnormalities, the rates were higher in the observation group than in the control group (P < 0.001). While subgroups comparisons showed that the complication rates were higher in the carrier and minor groups than in the control group, the differences between the intermediate group and the control group were significant only in three areas: Electrocardiograph (GDM), hypertensive disorders of pregnancy, and abnormal liver function, as detailed in Table 1. Among them, the main types of ECG abnormalities included sinus tachycardia, sinus bradycardia, sinus arrhythmia, premature atrial or ventricular beats, and atrioventricular block, as shown in Table 2.

4. Comparison of delivery outcomes

Regarding the incidences of preterm labor, postpartum hemorrhage and cesarean section, the rates were higher in the total observation group, carrier group and minor group than in the control group (P < 0.001), while there was no significant difference between the intermediate type group and the control group, as detailed in Table 1. The main reasons for cesarean section were fetal distress, abnormal labor, and chorioamnionitis, as shown in Table 3.

5. Comparison of neonatal outcomes

The 1-min Apgar score was slightly lower in the total observation group, the carrier group, and the minor group than in the control group (P < 0.05). Additionally, neonatal weight was lower in the total observation group and intermediate group than in the control group (P < 0.01). In the comparison of hemoglobin within 24 hours of birth, the levels were lower in the observation group and all subgroups than in the control group (P < 0.01), as shown in Figure 4.

Discussion

The global prevalence of thalassemia ranges from 2.5–25.0%, with a gene carrier rate of 1.7%. In China, Guangdong, Guangxi, Hainan and Sichuan are areas with a high prevalence of thalassemia, of which Guangxi has one of the highest rates of thalassemia carriage, up to 25%. Wang Liang et al. showed that α-thalassemia is currently the most common type of thalassemia within Guanxi. [5–6] The following deletion types of α-thalassemia genes have been identified in the population: -α3.7, -α4.2, -α2.7, -SEAI, -THAI, -FILI, -HWI, -11.1. However, the common nondeletion types of α-thalassemia genes are Hb CS, Hb QS, Hb WS. α-Thalassemia is clinically classified according to the number of defects in the α-genes. There are four types of α-thalassemia: carrier, minor, intermediate (HBH disease) and severe (hemoglobin Bart's hydrops fetalis). Among them, α-thalassemia major leads to Bart's edema in the fetus, which often results in intrauterine death in the middle or late stages of pregnancy or a few hours after delivery. [7–8] Therefore, there are no patients with alpha-thalassemia major in the population.

The distribution of the type of thalassemia, a common hereditary disease, has regional and ethnic differences. Understanding the characteristics of the genotype distribution in the region where it is located is beneficial to the prevention and control of thalassemia and genetic counseling work in the region. In this study, the α-thalassemia mothers were overrepresented by the Han and Zhuang ethnic groups, which is in line with the distribution of the local population in Guanxi by ethnicity. We detected a total of 25 genotypes, the most common of which were -SEA/oaa (673 cases, 49.2%), -α3.7/oaa (273 cases, 20.0%) and aCSα/aα (153 cases, 11.2%). This is consistent with the findings of Wang Liang [6], Lu Heng [9] and Wei Shuai [10] on the distribution of α-thalassemia genotypes in Guanxi.

In pregnant women with thalassemia, the maternal circulating blood volume increases during pregnancy, forming gestational anemia. At the same time, due to the increased demand for various nutritional elements, such as iron and protein, for fetal growth and development, maternal hemolytic anemia will become serious. The high iron load in the body is high due to chronic hemolysis and the fact that anemia leads to a decrease in hepatic iron-regulating hormone levels, which increases intestinal iron absorption and further aggravates the iron load[11]. This causes serum ferritin levels to be higher in affected pregnant women than in non-affected pregnant women, but maternal serum ferritin levels still decrease with increasing gestational weeks as the fetal demand increases. In our study, the hemoglobin level in the experimental group was lower than that in the control group regardless of the gestational period, with the lowest hemoglobin level occurring in the intermediate group; however, the serum ferritin level showed a rise. For both indicators, the decrease with gestation was also most significant in the intermediate group. This may be related to the fact that pregnancy may induce the hemolytic mechanism of thalassemia, thus aggravating anemia. In particular, thalassemia carriers should theoretically be no different from normal people; however, our results showed that there was no significant difference between the carrier group and the control group in the first and second trimesters, but the anemia condition of the carrier group in the third trimester was heavier than that of the control group. We speculate that pregnancy is in a chronic inflammatory immune state, and inflammatory cytokines may affect iron metabolism, inhibit the proliferation of red blood cells, shorten the life span of red blood cells, and eventually lead to the aggravation of anemia. Therefore, it has been suggested that pregnancy status may be one of the factors changing the phenotype of thalassemia. All of this suggests that we should pay special attention to the hemoglobin and serum ferritin levels of pregnant women with thalassemia and routinely recommend supplementation with folic acid and vitamin B12, as well as administration of blood transfusions when necessary in patients with severe anemia, recurrent infections, splenomegaly and fetal growth restriction.

In pregnant women with thalassemia, prolonged anemia and iron overload due to hemolysis can affect the function of various systems and organs. If iron is deposited in myocardial cells causing cellular damage, this can lead to heart failure and arrhythmias [13–14], while chronic anemia can also...
lead to myocardial ischemia and electrocardiographic changes [15–16]. Excess iron can also mediate islet β-cell damage and alter insulin synthesis and secretion, leading to insulin resistance [17–18] and ultimately abnormal glucose metabolism [19]. Several studies [20–23] found that severe anemia and serum ferritin levels were significantly associated with the incidence of hypertensive disorders, and Wang Yanxia et al [24] also indicated that high iron load causes the body to experience oxidative stress and increased vasoconstriction, leading to the development of hypertensive disorders of pregnancy. If a large amount of iron is deposited in the thyroid gland, chronic fibrotic changes in its substance can occur, and free iron can catalyze the formation of highly reactive oxygen radicals, leading to cytotoxicity and thyroid functional impairment [25–26]. Although the majority of pregnant women without comorbidities have normal liver biochemical parameters [27], the abnormal nucleoprotein chain in thalassemic women leads to damage to the body's red blood cells and increases production of bilirubin, causing hyperbilirubinemia, which in turn affects the patient's liver function [28]. In this study, we found that the incidence of pregnancy comorbidities was higher in both the observation and control groups, which is consistent with the results of previous studies. It has therefore been suggested that pregnancy should not be recommended for women with iron overload. Pregnant women with thalassemia should be monitored in the early stages of pregnancy by means of regular tests of cardiac and liver function and thyroid function and close monitoring of blood glucose and blood pressure, especially for patients who require multiple transfusions. In particular, pregnant women with thalassemia who are severely anemic should still be alerted to a decline in cardiac reserve after delivery, as well as to outbreaks of liver or thyroid abnormalities.

In terms of delivery outcome, it can be concluded from the results that the rates of cesarean section, preterm labor, and postpartum hemorrhage were all higher in the observation group than in the control group, and the most common causes of cesarean section were fetal distress and abnormal labor, which may be due to long-term chronic anemia and insufficient blood circulation to the uterus and placenta, which affects the contraction of the uterine muscles and leads to postpartum hemorrhage [29]. This is consistent with the results of a study by Luo Li and Liang Xu Xia [30]. It has also been reported that anemia in pregnancy can result in inadequate production of antibodies in pregnant women[31], reducing their immune function and predisposing them to infections. Thalassemia is not a surgical indication for cesarean section, and the choice of delivery method for pregnant women with combined thalassemia should be individualized, with clear obstetric indications for cesarean section.

The effects of anemia during pregnancy on the fetus have been shown to cause intrauterine ischemia and hypoxia, restricted growth and development due to inadequate nutrient supply, and increased incidence of low birth weight. A study by Pang Ting and Guo Xuefeng et al [32] showed that maternal comorbidities with minor alpha-thalassemia may increase the risk of lower birth weight in newborns. A study by Huang Xiaochun and Qiu Xiaojie et al. [33] also showed that the presence of thalassemia in both or either parent increased the risk of low birth weight in newborns. This is consistent with the results of our study showing that the neonatal weight was lower in the observation group than in the control group. The neonatal Apgar scores are usually assessed clinically, with the 1-minute Apgar score being more representative of the status of the newborn in utero. Several studies have suggested that the degree of maternal anemia affects the Apgar score of the newborn, with more severe anemia leading to a higher risk of neonatal asphyxia. In this study, the 1-min Apgar scores were slightly but significantly lower in the carrier and minor groups than in the control group. The fetus receives all the iron it needs for growth and development from the mother through the placenta. When the pregnant woman has different degrees of anemia and insufficient iron reserves, the hematopoiesis and iron reserves of the fetus are also affected to varying degrees, manifesting as a decrease in hemoglobin and serum ferritin in the newborn [34]. Recent studies have also shown [35] that both iron and iron saturation in the cord blood of newborns are reduced in maternal anemia. Women with thalassemia in combination with pregnancy are more anemic during pregnancy than anemic women without thalassemia, so theoretically, newborns delivered by women with thalassemia should have lower hemoglobin levels, which is also consistent with the comparative results of the hemoglobin of newborns delivered in this study at 24 hours of life.

In this study, we suggest that the pregnancy status, delivery outcomes and neonatal outcomes of pregnant women with thalassemia are somewhat different from those of normal pregnant women; however, this study is a retrospective study, and the different dietary habits of different pregnant women may affect their pregnancy status to some extent. In addition, due to the low incidence of intermediate α-thalassemia, there were only 39 pregnant women with intermediate thalassemia in this study, so this group had a smaller sample size than the other groups, which may lead to bias and certain limitations in the results. In future studies, the sample size should be further increased to draw more objective and accurate conclusions.

**Conclusion**

Pregnant women with intermediate α-thalassemia have the lowest hemoglobin level and the highest serum ferritin level, and both indicators have the greatest decline during pregnancy; pregnant women with α-thalassemia have higher rates of pregnancy complications, low birth weight and low hemoglobin levels than pregnant women without thalassemia. Pregnant women with α-thalassemia should receive a standardized maternal examination during pregnancy, monitoring of pregnancy-related indicators at the right time, and timely detection and correction of abnormal indicators to prevent and reduce adverse pregnancy outcomes. Pregnancy-related indicators should be monitored and corrected in a timely manner to prevent and reduce adverse pregnancy outcomes.

**Abbreviations**

ECG: Electrocardiograph
GDM: Gestational Diabetes Mellitus
OGTT : 75g oral glucose tolerance test

Declarations

Ethics approval and consent to participate

The study had been performed in accordance with the Declaration of Helsinki. The study was approved by the ethics review board of the First Affiliated Hospital of University of South China. The study informed consent was obtained from all subjects.

Consent for publication

Not applicable.

Availability of data and materials

These data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Lihong Pang conceived the original idea and wrote the proposal. Yi Li, Yuanyuan Feng and Zhiwei Zhu designed the study. Yi Li, Yuanyuan Feng, Zhiwei Zhu, Yiyun Wei, Jing Huang, Hui Chen, Changqiang Wei and Kaiyi Wei organized the data collection. Yi Li, Yuanyuan Feng and Zhiwei Zhu analyzed the data. Yi Li and Lihong Pang wrote the manuscript for publication. All authors contributed to editing the manuscript and provided critical feedback and approved the final manuscript.

Acknowledgments

Thanks to Dr. Dong Yang for his help in statistics and submission process.

References


## Table 1 Comparison of pregnancy complications and delivery outcomes

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<th>Intermediate (%) (n=39)</th>
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Notes: Bold indicates a significant difference among groups with $p < 0.05$.

## Table 2 The types of abnormal ECG
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<td>Minor</td>
<td>188</td>
<td>82(43.6%)</td>
<td>23(12.2%)</td>
<td>64(34.0%)</td>
<td>19(10.1%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>7</td>
<td>4(57.1%)</td>
<td>0(0.0%)</td>
<td>2(28.6%)</td>
<td>1(14.3%)</td>
</tr>
<tr>
<td>Control group</td>
<td>65</td>
<td>28(43.1%)</td>
<td>9(13.8%)</td>
<td>25(38.5%)</td>
<td>3(4.6%)</td>
</tr>
</tbody>
</table>

Table 3 The causes of cesarean section

<table>
<thead>
<tr>
<th>Groups</th>
<th>Numbers</th>
<th>Causes of cesarean section</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fetal distress</td>
<td>Abnormal labor stage</td>
<td>Chorioamnionitis</td>
<td>Others</td>
</tr>
<tr>
<td>Carrier</td>
<td>135</td>
<td>65(48.1%)</td>
<td>20(14.8%)</td>
<td>9(6.7%)</td>
<td>41(30.4%)</td>
</tr>
<tr>
<td>Minor</td>
<td>239</td>
<td>124(51.9%)</td>
<td>44(18.4%)</td>
<td>14(5.9%)</td>
<td>57(23.8%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16</td>
<td>5(31.3%)</td>
<td>1(6.3%)</td>
<td>2(12.5%)</td>
<td>8(50.0%)</td>
</tr>
<tr>
<td>Control group</td>
<td>61</td>
<td>20(32.8%)</td>
<td>8(13.1%)</td>
<td>17(27.9%)</td>
<td>16(26.2%)</td>
</tr>
</tbody>
</table>

Figures

Figure 1
The distribution of ethnicity
Figure 2

The distribution of genotype

Total = 1371
Figure 3

The comparison of hemoglobin and serum ferritin. Comparison of hemoglobin in first trimester (A), comparison of hemoglobin in second trimester (B), comparison of hemoglobin in third trimester (C), comparison of the decline in hemoglobin during pregnancy (D), comparison of serum ferritin in first trimester (E), comparison of serum ferritin in second trimester (F), comparison of serum ferritin in third trimester (G), comparison of the decline in serum ferritin during pregnancy (H). p values were calculated with the Kruskal-Wallis H test. * means P < 0.05, ** means P < 0.01, *** means P < 0.001.

Figure 4

The comparison of neonatal outcomes. Comparison of 1-min Apgar score (A), comparison of neonatal weight (B), comparison of neonatal HGB (C). p values were calculated with the Kruskal-Wallis H test. * means P < 0.05, ** means P < 0.01, *** means P < 0.001.