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ORIGINAL RESEARCH

Investigation of the Influence of Deletional and Non-Deletional Hemoglobin H Disease on Pregnancy Outcomes

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Objective: The study aimed to provide clinical evidence regarding the perinatal management of HbH disease by comparing and analyzing blood routine, anemia characteristics, and their influence on pregnancy outcomes in patients with common deletional and non-deletional HbH disease at various pregnancy stages.

Patients and Methods: From May 2017 to October 2023, a comparative analysis was conducted on pregnant women undergoing treatment at the Second Affiliated Hospital of Guangxi Medical University and the Second Nanning People's Hospital. The study included 42 cases of deletional HbB disease and 32 cases of non-deletional HbH disease. The study assessed blood routine, anemia, and pregnancy outcomes during early and late pregnancy.

Results: In the deletional group, there was a significantly higher incidence of moderate anemia during both early and late pregnancy compared to the non-deletional group. Moreover, the deletional group exhibited a significantly lower mean corpuscular volume (MCV) during early and late pregnancy and mean corpuscular hemoglobin (MCH) during late pregnancy, with statistically significant differences ($p<0.05$) compared to the non-deletional group. Additionally, the non-deletional group had a significantly higher incidence of postpartum blood transfusion, fetal growth restriction (FGR), and low birth weight (LBW) compared to the deletional group, with a statistically significant difference ($p<0.05$).

Conclusion: Pregnant patients with alpha-thalassemia HbH disease and non-deletional HbH disease commonly experience moderate anemia, increasing the risk of adverse pregnancy outcomes, particularly in non-deletional HbH disease cases where negative outcomes are more prevalent. It is crucial to enhance perinatal monitoring and intervention for pregnant women with HbH disease, including regular assessment of hemoglobin (Hb) levels, MCV, and MCH, and implementing measures to manage anemia to mitigate adverse pregnancy outcomes effectively.

Keywords: hemoglobin H disease, deletional HbH, non-deletional HbH, perinatal care, pregnancy outcomes

Introduction

Alpha-thalassemia, commonly known as Mediterranean anemia, results from the partial or complete inhibition of α-globin peptide chain synthesis, leading to hereditary hemolytic anemia due to insufficient hemoglobin (Hb) production. This autosomal recessive condition is globally the most prevalent single-gene genetic disorder.[1] The clinical presentation of thalassemia varies significantly, with the severity directly linked to the reduction in globin chains and the correlation with gene copy number.[2–4] Alpha-thalassemia is prevalent in regions along the Mediterranean coast, Africa, and Southeast Asia, exhibiting distinct racial characteristics and regional distribution disparities.[5] In China, the condition is predominantly found in the southern region of the Yangtze River, with the highest prevalence in Guangdong, Guangxi,

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and Hainan.[1] Hemoglobin H disease (HbH), a specific type of α-thalassemia, is considered the most severe among the surviving phenotypes.[6] The genotypes of HbH disease mainly include deletional types ($-\alpha^{3.7}/-$, $-\alpha^{4.2}/-$) and non-deletional types ($\alpha^{WS}\alpha/-$, $\alpha^{CS}\alpha/-$, $\alpha^{QS}\alpha/-$, $\alpha^{CS}\alpha/\alpha^{CS}\alpha$, $\alpha^{QS}\alpha/\alpha^{QS}\alpha$, $\alpha^{CS}\alpha/\alpha^{QS}\alpha$). The clinical manifestations and hematological parameters of the non-deletional type are more severe than those of the deletional type.[1]

Throughout pregnancy, the combination of blood dilution and worsening anemia can lead to various risks for women, such as anemic heart disease, thrombosis, fetal loss, fetal growth restriction, fetal distress, premature birth, and neonatal asphyxia. Adverse pregnancy outcomes not only compromise the health of pregnant women but also escalate their economic burden and strain medical resources. Therefore, the implementation of appropriate perinatal interventions is imperative for reducing these adverse outcomes.This study aimed to examine the influence of Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and the administration of blood transfusions during various stages of the perinatal period on pregnancy outcomes in individuals with common and non-common types of HbH disease. This study is important as it seeks to offer clinical insights that could enhance the management of HbH disease during the perinatal period, thereby providing valuable information for healthcare providers. Previous research has explored the impact of HbH disease on pregnancy outcomes, revealing an increased risk of complications such as oligohydramnios, fetal growth restriction (FGR), and fetal distress.[7] Additionally, this study sought to compare pregnancy outcomes between common deletional types and non-deletion types in HbH disease classification by incorporating data from another medical center for comprehensive analysis.

Patients and Methods

Patients

We enrolled 42 patients diagnosed with HbH disease who received treatment at the Second Affiliated Hospital of Guangxi Medical University and the Second People's Hospital of Nanning between May 2017 and October 2023. Of these, 22 cases (29.73%) presented with $\alpha^{3.7}/-$, and 20 cases (23.03%) exhibited $\alpha^{4.2}/-$. Furthermore, the study included 32 patients with non-deletional HbH disease, comprising 12 cases (16.22%) of $\alpha^{WS}\alpha/-$, 16 cases (21.62%) of $\alpha^{CS}\alpha/-$, and 4 cases (5.40%) of $\alpha^{QS}\alpha/-$. The participants were all single pregnant women.

Methods

This study is a retrospective study. This research followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University and the Second Nanning People's Hospital. Informed consent was obtained from the participating patients after explanation of the nature, risks, and benefits of the study.

The subjects are patients who were diagnosed and treated at the Second Affiliated Hospital of Guangxi Medical University and the Second Nanning People's Hospital.

All pregnant women in this cohort denied any history of blood transfusion prior to pregnancy during the medical history collection. Inclusion criteria encompassed confirmed HbH disease, regular prenatal check-ups, absence of fetal malformations, no cognitive impairment or history of mental illness, and informed consent. Exclusion criteria included multiple pregnancies, other types of thalassemia, hematological system diseases, immunological diseases, heart disease, chronic kidney disease, fetal malformation, and induced abortion/miscarriage.

Diagnostic Criteria

1. HbH disease, also referred to as intermediate type α Thalassemia, results from three α genetic defects that cause a severe reduction in chain synthesis.[1,3] Common genotypes include deletional types ($\alpha^{3.7}/-$, $\alpha^{4.2}/-$) and non-deletional types ($\alpha^{WS}\alpha/-$, $\alpha^{CS}\alpha/-$, $\alpha^{QS}\alpha/-$, $\alpha^{CS}\alpha/\alpha^{CS}\alpha$, $\alpha^{QS}\alpha/\alpha^{QS}\alpha$, $\alpha^{CS}\alpha/\alpha^{QS}\alpha$).
2. Gestational anemia is identified in pregnant women with peripheral Hb levels below 110 g/L, with sub-classifications including mild anemia (100–109 g/L), moderate anemia (70–99 g/L), and severe anemia (40–69 g/L).[8]
3. Preterm birth (PTB) is childbirth occurring between 28 weeks and less than 37 weeks of pregnancy.[8]
4. A low birth weight (LBW) is a fetus weighing less than 2500g at birth.[8]

5. Fetal distress refers to a range of symptoms indicating the potential threat to the fetus's health or life due to acute or chronic hypoxia in the uterus.[8]
6. Neonatal asphyxia is characterized by the following criteria: a 5-minutes Apgar score of ≤ 7, indicating ineffective establishment of breathing; umbilical artery blood gas analysis showing a pH<7.15; exclusion of other causes for low Apgar scores; and the presence of high-risk factors that could lead to asphyxia before delivery. The first three criteria are mandatory, while the fourth serves as a reference standard.[8]
7. Fetal growth restriction (FGR) is an estimated fetal weight falling below the 10th percentile for the corresponding gestational age.[9]

Methods and Observational Indicators

Pregnant women who met the inclusion criteria were assigned to either a deletion or non-deletion group for the study. Complete blood count tests were performed in both early and late pregnancy, with results obtained before 13 weeks of gestation selected for early pregnancy and the most recent results prior to delivery selected for late pregnancy. The study compared the blood routine results and pregnancy outcomes in early and late pregnancy, including HB levels, anemia severity, MCV, MCH, gestational weeks, newborn birth weight, cesarean section, blood transfusion during pregnancy, oligohydramnios, postpartum hemorrhage (PPH), postpartum blood transfusion, FGR, PTB, fetal distress, LBW, and neonatal asphyxia.Despite grouping the non-deletional genotypes together, we recognize that these genotypes (such as $\alpha^{CS}\alpha/\alpha^{CS}\alpha$, $\alpha^{QS}\alpha/\alpha^{QS}\alpha$, and $\alpha^{CS}\alpha/\alpha^{QS}\alpha$) may exhibit significant differences in clinical presentation and hematological parameters, which could impact the formulation of management strategies. Therefore, individualized management tailored to the different non-deletional genotypes will be necessary in clinical practice.

Statistical Analysis

The research data were analyzed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) statistical software. The mean ± standard deviation ($\bar{x} \pm s$) was employed for econometric data conforming to or approximating a normal distribution. A *t*-test was utilized to compare indicators between the two groups, with a significance level of $p<0.05$ indicating statistical significance. Percentage (%) was used to express count data and analyzed using the χ^2 test. Fisher's exact test was applied when the expected count was less than 5, and a significance level of $p<0.05$ denoted statistical significance.

Results

No statistically significant differences in age, body mass index (BMI), pregnancies and parity were found between the two groups ($p>0.05$) as illustrated in Table 1.

The deletional and non-deletional groups exhibited moderate anemia as their primary characteristic. The deletional group demonstrated significantly higher rates of moderate anemia in early and late pregnancy than the non-deletional group. In contrast, the incidence of severe anemia was lower than that of the non-deletional group, with statistical significance ($p<0.05$). However, there was no statistically significant difference in Hb levels between the two groups during early and late pregnancy ($p>0.05$). The MCV in the first and third trimesters and the MCH in the third trimester were significantly lower in the deletional group compared to the non-deletional group, with the statistically significant differences ($p<0.05$), as illustrated in Table 2.

Table 1 Comparisons of General Materials Between Deletional and Non-Deletional Groups ($\bar{x} \pm s$)

General Materials	Deletional (42 cases)	Non-Deletional (32 cases)	t	P-value
Age (year)	30.40 ± 5.30	28.91 ± 5.58	1.178	0.243
BMI (kg/m^2)	21.07 ± 2.74	20.73 ± 2.04	0.595	0.554
Pregnancies	2.61 ± 1.51	2.21 ± 1.21	1.285	0.203
Parity	1.76 ± 0.97	1.59 ± 0.68	1.216	0.474

Abbreviation: BMI, body mass index.

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Table 2 Comparisons of HB, MCV, and MCH Between Deletional and Non-Deletional Groups [N (%) or $\bar{x} \pm s$]

	Deletional (42 cases)	Non-Deletional (32 cases)	t/χ^2	P-value
HB (g/L)				
1st trimester	88.59 ± 10.61	87.86 ± 20.53	0.2	0.854
Normal HB	1 (2.38)	6 (18.75)	22.89	<0.001
Mild anemia	3 (7.14)	6 (18.75)		
Moderate anemia	38 (90.48)	13 (40.62)		
Severe anemia	0 (0.00)	7 (21.88)		
3rd trimester HB	90.19 ± 11.83	90.42 ± 18.16	−0.066	0.947
Normal HB	1 (2.38)	3 (9.38)	8.53	0.028
Mild anemia	5 (11.91)	8 (25.00)		
Moderate anemia	35 (83.33)	17 (53.12)		
Severe anemia	1 (2.38)	4 (12.50)		
MCV (fl)				
1st trimester	62.06 ± 7.62	70.02 ± 7.61	−4.451	<0.001
3rd trimester	64.46 ± 7.93	74.71 ± 8.80	−5.254	<0.001
MCH (pg)				
1st trimester	20.06 ± 8.19	20.09 ± 1.80	−0.2	0.984
3rd trimester	18.96 ± 2.59	20.77 ± 1.86	−3.336	0.001

Abbreviations: HbH, Hemoglobin H disease; HB, Hemoglobin; MCV, Mean corpuscular volume; MCH, Mean corpuscular hemoglobin.

Table 3 Comparisons of Pregnancy Outcomes Between Deletional and Non-Deletional Groups [N (%) or $\bar{x} \pm s$]

Pregnancy Outcomes	Deletional (42 cases)	Non-Deletional (32 cases)	t/χ^2	P-value
Neonatal weight (g)	3007.26 ± 332.69	2835.63 ± 515.12	1.737	0.087
Delivery (day)	273.33 ± 8.29	272.53 ± 8.96	0.398	0.629
Cesarean section	25 (59.52)	15 (48.88)	1.17	0.349
Peripartum blood transfusion	1(2.38)	4 (12.50)	2.952	0.159
Oligohydramnios	9 (21.43)	9 (28.13)	0.442	0.589
FGR	9 (21.43)	14 (43.75)	4.225	0.047
PPH	0 (0.00)	1 (3.13)	5.682	0.432
Postpartum transfusion	1 (2.38)	6 (18.75)	5.682	0.001
PTB	2 (4.76)	2 (6.25)	0.079	0.647
Fetal distress	5 (11.90)	7 (21.88)	1.329	0.342
LBW	0 (0.00)	7 (21.88)	10.147	0.002
Neonatal asphyxia	0 (0.00)	1 (3.13)	1.33	0.432

Abbreviations: FGR, Fetal growth restriction; PPH, postpartum hemorrhage; PTB, preterm birth; LBW, low birth weight.

As shown in Table 3, we did not collect relevant evidence regarding fetal edema, and therefore did not discuss it in the results, the deletional group exhibited a significantly lower incidence of postpartum blood transfusion, FGR, and LBW than the non-deletional group, with statistical significance (p<0.05).

Discussion

Guangxi is a high-risk region for thalassemia, particularly α-Mediterranean anemia, a prevalent single-gene inherited disease.[1] This condition encompasses static, mild, intermediate (HbH disease), and severe types, distinguished by the degree of gene

function loss.[2,4] While static and mild types may be asymptomatic, laboratory tests typically reveal microcytic hypochromic anemia.[1] Severe thalassemia often results in intrauterine fetal demise due to profound hypoxia.[1,3] HbH disease represents the most severe surviving phenotype of α-Mediterranean anemia.[6] In HbH disease, the inadequate production of α-globin chains leads to an excess of β chains, resulting in the formation of unstable HbH. The instability of HbH causes it to decompose into free β chains, which then form sediments, damage red blood cells, and trigger hemolytic anemia.[1] The study revealed variations in anemia rates between deletional and non-deletional types in MCV, MCH, and differing severity levels. Non-deletional anemia displayed diversity, with varying degrees of anemia rates. Nonetheless, both groups exhibited moderate anemia during pregnancy, aligning with prior research.[5,10]

During pregnancy, the increase in blood volume and its dilution can exacerbate anemia, leading to persistent hypoxemia and increasing the risk of adverse pregnancy outcomes.[7] In Guangxi, HbH patients exhibit distinct genetic profiles, with the deletional type predominant; however, the severity of anemia varies significantly across different genotypes.[11] Patients with HbH disease typically experience moderate anemia during pregnancy, which can impact the mother and fetus differently. Although some pregnant women experienced anemia, no cases of congestive heart failure caused by anemia were observed. Establishing the optimal Hb level for achieving favorable pregnancy outcomes is crucial. A comprehensive assessment is necessary to determine the need for blood transfusion to maintain Hb levels above 80g/L,[5] while other studies recommend maintaining levels above 100g/L to support fetal growth.[12] It is essential to consider the pros and cons of frequent blood transfusions to improve pregnancy outcomes.[10] Determining the optimal Hb level still requires larger sample sizes and multicenter studies. This study found no significant difference in Hb levels between deletion and non-deletional types. However, there was a notable difference in MCV and MCH, with deletional types exhibiting lower levels than non-deletional types, consistent with previous research.[13] The lower levels of MCV and MCH in deletion type compared to non-deletion type may be due to the functional loss of three α-genes resulting in reduced α-globin production. Instead, the non-deletion type consists of two functional deletions of α-genes and one point mutation affecting the structure of the α-globin chain or two high-functioning point mutations involving α2 genes.[1] The number of gene deletions in non-deletional anemia is lower than in the deletional types, resulting in lower MCV and MCH than in deletional types. Non-deletional anemia presents higher rates of normal Hb levels, mild anemia, and severe anemia during pregnancy compared to deletional anemia. Therefore, the decision to undergo a blood transfusion during pregnancy requires careful consideration. The postpartum blood transfusion rate is lower in deletional anemia than in non-deletional anemia, possibly due to increased blood volume during pregnancy, exacerbation of anemia through blood dilution, and further aggravation of anemia due to blood loss during delivery, leading to an increased need for postpartum blood transfusion.The indications for peripartum and postpartum transfusion are: HB < 70 g/L.

Pregnant women with iron deficiency demonstrate lower rates of postpartum blood transfusion, fetal growth restriction, and low birth weight compared to non-deletional women. This difference may be attributed to the severity of anemia in non-deletional HbH disease. No significant variances were observed in cesarean section rate, oligohydramnios rate, postpartum hemorrhage rate, preterm birth rate, fetal distress rate, and neonatal asphyxia rate between the two groups. However, fetal growth restriction and low birth weight were most prevalent in the non-deletional group. The study by Mitsuda et al suggests that abnormal Hb concentrations, whether low or high, may be associated with fetal growth restriction.[14] Research has consistently shown that reduced Hb levels can hinder placental angiogenesis, diminish fetal oxygen delivery, and lead to FGR and LBW.[15,16]

Conclusions

In summary, based on our data, HbH disease is associated with an increased risk of adverse pregnancy outcomes, particularly in non-deletional types. More severe anemia in early pregnancy is linked to a higher likelihood of requiring blood transfusion during delivery, as well as a greater incidence of fetal growth restriction and low birth weight. These findings suggest that different management strategies may be necessary for patients with deletional and non-deletional HbH disease during perinatal care.For the deletional HbH disease group, it is recommended to regularly monitor hemoglobin levels and red blood cell indices during pregnancy to timely identify and treat anemia, and to perform blood transfusions when necessary to improve oxygen supply to both the mother and fetus. Additionally, enhanced monitoring of fetal growth should be implemented to ensure a healthy pregnancy.For the non-deletional HbH disease

group, closer monitoring during pregnancy is advised, particularly regarding postpartum blood transfusion needs and assessments of fetal growth. More proactive interventions should be considered in late pregnancy, such as appropriate nutritional support and necessary blood transfusions, to reduce the incidence of FGR and LBW. Furthermore, individualized management plans should be developed to adjust treatment strategies based on the specific circumstances of each patient, optimizing perinatal outcomes.

Management strategies for patients with different types of HbH disease should be personalized according to their clinical presentations and risk factors to improve perinatal health outcomes.Furthermore, the development of predictive models for targeted prevention or treatment can significantly reduce the risk of adverse pregnancy outcomes. Although there is no consensus on the optimal Hb level during pregnancy, addressing this issue remains a priority for healthcare professionals.

Data Sharing Statement

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

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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