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Hematological indicators and their impact on maternal and neonatal outcomes in pregnancies with thalassemia traits

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Abstract

Objectives: The aim of this study is to compare the obstetric, neonatal, and hematological indicators of pregnant women with thalassemia traits with those of pregnant women without such traits.

Methods: This retrospective cohort study was conducted from January 2017 to October 2023 at the Department of Obstetrics and Gynecology, The First Affiliated Hospital of Dali University. The study included 185 cases of thalassemia traits and 185 control cases. Data were analysis using the SPSS program (Version 27.0).

Results: Significant differences were observed in gravidity and parity histories ($p<0.05$). Significant differences were also observed in the rates of gestational diabetes mellitus (GDM), hypertensive disorder of pregnancy (HDP), cesarean delivery, adherent placenta, and anemia in the second and third trimesters following the number of RR (95 % CI): 2.182 (1.101–4.324), 9.000 (1.152–70.325), 2.091 (1.555–2.811), 3.401 (1.280–9.009), 4.222 (2.102–8.481), and 2.053 (1.476–2.855), respectively ($p<0.05$). However, no significant differences were noted in the rates of preterm birth, low birth weight, macrosomia, intrauterine growth restriction, fetal distress, fetal malformation, and stillbirth ($p>0.05$). Furthermore, significant differences were noted in the levels of hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW) during the first, second, and third trimesters ($p<0.05$).

Conclusions: As pregnancy progresses, the levels of Hb tend to decrease, while the MCH and RDW levels increase. On the other hand, the level of MCV remain the same overtime. Thalassemia traits are significantly associated with anemia during pregnancy, particularly in the second and third trimesters. Furthermore, thalassemia traits are related to an increased incidence of GDM, HDP, and cesarean delivery.

Keywords: hematological indicators; neonatal outcomes; obstetric outcomes; pregnancy complications; thalassemia

Introduction

Thalassemia is characterized by the absence or point mutation of the globin gene in hemoglobin, leading to impaired synthesis of globin peptide chains. This results in insufficient hemoglobin production, ineffective erythropoiesis, hemolysis, and varying degrees of microcytic hypochromic hemolytic anemia, thereby decreasing the oxygen-carrying capacity of red blood cells. Chronic anemia in thalassemia can lead to excessive iron absorption. This can damage the liver, spleen, heart, and endocrine systems [1–3].

The World Health Organization (WHO) published the World Report on Hemoglobinopathies Epidemiology in 2008, revealing that among 229 countries, approximately 71 % face issues with hemoglobin diseases, affecting 330,000 newborns annually. Of these hemoglobin diseases, sickle cell anemia accounts for 83 %, while thalassemia constitutes 17 %. Globally, around 7 % of pregnant women are carriers of hemoglobin diseases (including α-thalassemia, β-thalassemia, Hb C, Hb D-Punjab, and Hb E), and over 1 % of couples are at risk [4].

In 1925, thalassemia was first described and identified in the Mediterranean population by an Italian physician, who reported five cases exhibiting unique symptoms of microcytic hypochromic hemolytic anemia. This specific form of anemia was subsequently named thalassemia. Thalassemia represents the most prevalent autosomal recessive monogenic genetic disease globally, affecting the highest cumulative number of individuals. It is estimated that approximately 350 million

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people worldwide are carriers of the thalassemia gene [5]. Of these carriers, around 260 million carry the α-thalassemia gene, constituting approximately 5 % of the global population, while approximately 80–90 million carry the β-thalassemia gene, accounting for about 1.5 % of the global population [6, 7].

Thalassemia is widely distributed, prevalent not only in Mediterranean coastal regions but also across Northern Africa, the Middle East, Southeast Asia, and southern China. It is the most common and highest incidence single-gene genetic disease worldwide [8]. The Southeast Asian population, in particular, exhibits a high incidence of α-thalassemia, β-thalassemia, Hb E, and Hb CS [9–13].

Based on the Zeng and Huang study conducted in 1987, the national prevalence of α-thalassemia and β-thalassemia was determined to be 0.66 and 2.64 %, respectively, across several laboratories [14]. Recent large-scale surveys on thalassemia conducted in various regions of China have indicated continued high incidence rates [15, 16]. Lai et al. reported an overall prevalence of 7.88 % for β-thalassemia and 2.21 % for α-thalassemia [17]. In Southern China, including Guangxi, Guangdong, Hainan, Yunnan, Sichuan, Chongqing, Fujian, and other areas, carrier rates vary significantly, ranging from 3.3 to 24.07 %. Among these regions, Guangxi and Guangdong exhibit the highest incidence of thalassemia [17, 18].

Thalassemia is the most common and prevalent single-gene genetic disorder globally. Despite its widespread effect, effective curative treatments applicable in clinical practice remain elusive. The high cost of treatment and challenges in finding suitable donors further complicate management efforts. This disease imposes a growing burden on healthcare systems and economies, contributing to significant psychological stress and substantial financial strain on the families of patients and society at large. Thalassemia presents serious public health challenges and can impede the development of a country. In China, treating severe thalassemia costs approximately RMB 1 million per case on average, often pushing affected families into poverty or back into poverty [19–22].

Thalassemia encompasses four primary types: α, β, δ, and δβ, with α and β-thalassemia being the most prevalent [23]. α-thalassemia is further categorized into four degrees: silent carrier, mild, intermediate, and severe. Silent carriers are asymptomatic and lead normal lives. Mild cases are healthy and asymptomatic, although they may experience mild anemia or microcytosis. Intermediate cases present with symptoms including anemia, fatigue, hepatosplenomegaly, and mild jaundice, typically developing these symptoms after infancy. Severe cases in fetuses often lead to fetal death due to severe edema during development or shortly after birth. β-thalassemia includes mild, intermediate, and severe forms. Mild cases may be asymptomatic or present with mild anemia. Intermediate cases indicate symptoms in early childhood like mild to moderate splenomegaly and mild bone changes. Severe cases experience progressive anemia starting 3–6 months after birth, necessitating lifelong transfusions and iron chelation therapy, leading to severe hepatosplenomegaly. Without proper treatment, these patients typically do not survive beyond the age of 5 [24–26].

As the global population expands and migrates, the number of thalassemia gene carriers rises, spreading the disease to diverse regions and making it a significant global public health concern affecting nearly every country worldwide. Effective strategies for prevention and control of adverse pregnancy outcomes, antenatal care enhancement for women of childbearing age, and enhancement of birth population quality need to be considered [25].

Most thalassemia-related studies in China have predominantly focused on Guangxi and Guangdong provinces. However, Yunnan stands out as the province with the largest number of minority nationalities in China, each with distinct customs and lifestyles. Geographically adjacent to Southeast Asian countries, which have high incidences of thalassemia, Yunnan presents a unique setting where various types of thalassemia with complex genetic underpinnings may affect individuals, particularly pregnant women [17–20]. Previous studies have often examined only specific subsets of hematological indicators or pregnancy outcomes, potentially leading to misdiagnoses among patients with mild thalassemia, who may be asymptomatic or experience mild anemia. Pregnancy can exacerbate symptoms, heightening adverse effects for both the mother and child. Consequently, research on pregnancy with mild thalassemia remains limited and controversial [21–26]. Therefore, the objective of this research was to assess the association between thalassemia traits and pregnancy outcomes among women without thalassemia, focusing on various adverse pregnancy outcomes and complications including gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), preeclampsia, eclampsia, intrahepatic cholestasis of pregnancy (ICP), placental abruption, hydramnios, oligohydramnios, premature rupture of membranes (PROM), chorioamnionitis, postpartum hemorrhage, cesarean delivery, meconium-stained amniotic fluid, adherent placenta, and anemia during pregnancy. Additionally, the objective of this study was to assess perinatal outcomes like fetal weight, preterm birth, low birth weight, macrosomia, intrauterine growth restriction (IUGR), neonatal asphyxia, fetal distress, fetal malformation, and stillbirth. Furthermore, the goal of the study was to indicate the combined effect of maternal blood routine indicators including hemoglobin (Hb), mean

corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW).

Materials and methods

The retrospective group study was approved by the Dali Institutional Review Board. From January 2017 to October 2023, data were collected from the In-patient Ward database at the Department of Obstetrics and Gynecology, The First Affiliated Hospital of Dali University. A total of 292 cases of pregnant women with thalassemia were diagnosed, of which 185 cases met the specified criteria, comprising of 112 cases of α-thalassemia trait and 73 cases of β-thalassemia trait. The process for screening cases among pregnant women is depicted in Figure 1. Additionally, 185 pregnant women without thalassemia were selected as the study participants of the control group. Data were retrieved from the electronic medical record system of the hospital.

Inclusion and exclusion criteria

The study group included patients diagnosed with α-thalassemia and β-thalassemia minor or those having the traits through genetic testing either before or during pregnancy. Conversely, the control group was randomly selected during the same period with a 1:1 ratio, based on similar baseline characteristics.

The inclusion criteria were as follows: (1) singleton pregnancies; (2) attendance for prenatal care and delivery at the F*** H; (3) no other medical or surgical conditions such as pre-gestational diabetes, chronic hypertension, or anemia from any causes; (4) availability of data on pregnancy outcomes; (5) no history of blood transfusion; and (6) pregnant women with good mental health, normal cognitive function, and high compliance.

The exclusion criteria were as follows: (1) pregnant women with other medical or surgical complications during pregnancy, like overt diabetes mellitus (DM), chronic hypertension, and renal disease; (2) fetuses affected by thalassemia major; (3) fetuses with significant chromosomal abnormalities or structural defects; (4) inadequate clinical data and pregnancy outcomes, including expectant mothers with unclear thalassemia status; (5) multiple pregnancies; (6) incomplete data.

The controls were randomly selected based on similar baseline characteristics and study duration as the study group. The inclusion and exclusion criteria for pregnant women without thalassemia were the same as for the study group.

Research methodology

This study uses a 1:1 sampling ratio, dividing the selected cases into two groups: the study group, comprising of pregnant women with thalassemia trait (α-thalassemia and β-thalassemia), and the control group, comprising of pregnant women without thalassemia. The following data are compared:

- Comparison of general data of pregnant women in both groups.
- Comparison of obstetric outcomes in both groups and subgroups.
- Comparison of neonatal outcomes in both groups and subgroups.
- Comparison of hematological indicators tests during different stages of pregnancy like Hb, MCV, MCH, and RDW in both groups and subgroups.

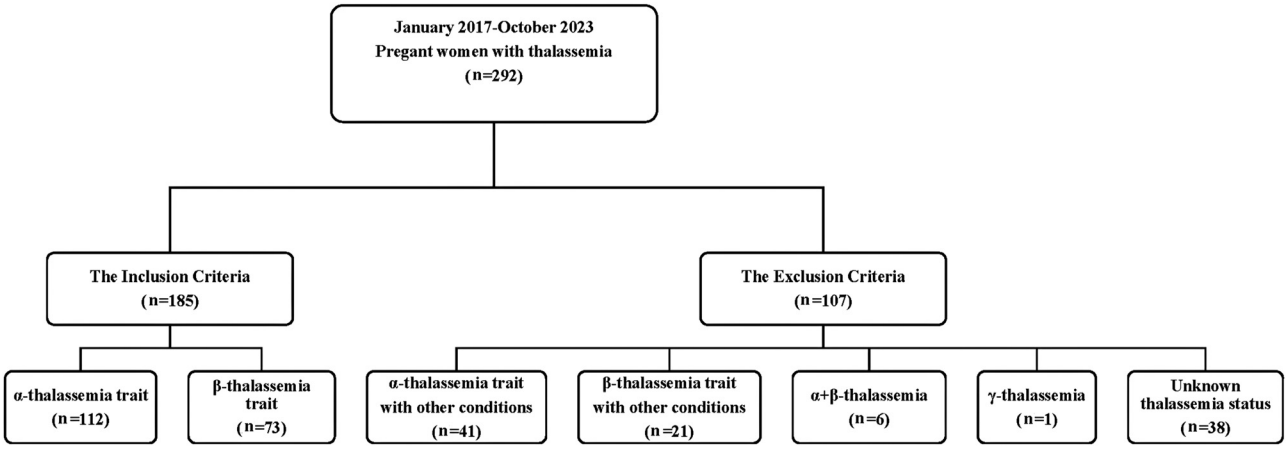

Figure 1: The screening process of pregnant women with thalassemia.

– Analysis of factors potentially influencing anemia in pregnant women with thalassemia.

Statistical methods

Statistical analyses were conducted using SPSS software, version 27.0 (SPSS Statistics for Windows, SPSS Inc., Chicago, IL, USA). In cases where quantitative data exhibit a normal distribution like Hb, MCV, MCH, and RDW, the results are presented as mean±standard deviation ($\bar{x} \pm SD$). Alternatively, if the data do not conform to a normal distribution, they are expressed using the median and interquartile range (M±IQR). When comparing two groups, a t-test for independent sample is used for analysis if the data are normally distributed and exhibit homogeneity of variance. Conversely, if the data do not follow a normal distribution and display heterogeneity of variance, a nonparametric test (Mann-Whitney U Test) for two independent samples is used. For comparisons among three groups, a one-way ANOVA is applied under conditions of normal distribution and homogeneity of variance. Alternatively, if the data do not adhere to a normal distribution and exhibit heterogeneity of variance, either the Kruskal-Wallis H Test or Friedman test is used. For categorical data like obstetric history, pregnancy complications in pregnant women, and adverse neonatal events, frequencies or percentages are used for presentation. Statistical analyses use the Chi-square test or Fisher's exact test, along with Pearson's Chi-square, as appropriate. Relative risk (RR) and its 95 % confidence interval (CI) are calculated to quantify the risk ratio of adverse pregnancy outcomes associated with thalassemia traits. The significance level is set to 0.05 for all analyses.

Results

Comparison of general information between thalassemia trait and control group of pregnant women

Table 1 displays the baseline characteristics of the study and control groups. There were no statistically significant differences observed in maternal age, maternal BMI, gestational age, history of abortions, history of fetal arrest, or history of stillbirth between the two groups. However, significant differences were noted in gravidity (p=0.021) and parity history (p=0.001) between the groups.

Table 1: Baseline characteristics of pregnant women with thalassemia trait and control group.

Characteristics	Study group (n=185)	Control group (n=185)	p-Value
Maternal age $\bar{x}$±SD	29.08 ± 4.91	28.66 ± 4.19	0.381
Maternal BMI (kg/m^2) $\bar{x}$±SD	26.97 ± 4.04	26.34 ± 3.37	0.103
Gestational age, n (%)			0.134
<36 weeks	14 (66.7 %)	7 (33.3 %)	
36 w–39 weeks	127 (51.2 %)	121 (48.8 %)	
≥40 weeks	44 (43.6 %)	57 (56.4 %)	
Gravidity, n (%)			0.021
1 time	68 (36.8 %)	91 (49.2 %)	
≥2 times	117 (63.2 %)	94 (50.8 %)	
Parity, n (%)			0.001
Nulliparity	108 (58.4 %)	143 (77.3 %)	
Primiparity	70 (37.8 %)	41 (22.2 %)	
Multiparity	7 (3.8 %)	1 (0.5 %)	
History of abortions, n (%)			0.085
Yes	77 (41.6 %)	60 (32.4 %)	
No	108 (58.4 %)	125 (67.6 %)	
History of fetal arrest, n (%)			0.156
Yes	13 (7 %)	6 (3.2 %)	
No	172 (93 %)	179 (96.8 %)	
History of stillbirth, n (%)			0.123
Yes	4 (2.2 %)	0 (0 %)	
No	181 (97.8 %)	185 (100 %)	

Comparison of obstetric outcomes between thalassemia traits and control group of pregnant women

Table 2 illustrates significant differences between the two groups in the prevalence rates of GDM, HDP, cesarean delivery, adherent placenta, anemia in the 2nd trimester, and anemia in the 3rd trimester, with corresponding RR and 95 % CI of 2.182 (1.101–4.324), 9.000 (1.152–70.325), 2.091 (1.555–2.811), 3.401 (1.280–9.009), 4.222 (2.102–8.481), and 2.053 (1.476–2.855), respectively. However, there were no statistically significant differences observed in the rates of preeclampsia, eclampsia, intrahepatic cholestasis of pregnancy (ICP), placental abruption, hydramnios, oligohydramnios, PROM, chorioamnionitis, postpartum hemorrhage, meconium-stained amniotic fluid, or anemia in the 1st trimester.

Comparisons of the obstetric outcomes between the sub groups α-thalassemia trait, β-thalassemia trait and control group

Table 3 presents the results of subgroup analysis concerning significant obstetric outcomes across various types of

Table 2: Obstetric outcomes between thalassemia trait and control group.

Outcome	Study group (n=185)	Control group (n=185)	p-Value	Relative risk (95 % CI)
GDM, n (%)	24 (13 %)	11 (5.9 %)	0.032	2.182 (1.101–4.324)
HDP, n (%)	9 (4.9 %)	1 (0.5 %)	0.020	9.000 (1.152–70.325)
Preeclampsia, n (%)	4 (2.2 %)	1 (0.5 %)	0.372	4.000 (0.451–35.449)
Eclampsia, n (%)	2 (1.1 %)	0 (0 %)	0.499	–
ICP, n (%)	4 (2.2 %)	3 (1.6 %)	1.000	1.333 (0.303–5.875)
Placental abruption, n (%)	6 (3.2 %)	4 (2.2 %)	0.751	1.500 (0.430–5.228)
Hydramnios, n (%)	1 (0.5 %)	2 (1.5 %)	1.000	0.500 (0.046–5.467)
Oligohydramnios, n (%)	13 (7 %)	10 (5.4 %)	0.668	1.300 (0.585–2.890)
PROM, n (%)	35 (18.9 %)	50 (27 %)	0.083	0.700 (0.478–1.024)
Chorioamnionitis, n (%)	30 (16.2 %)	31 (16.8 %)	1.000	0.968 (0.612–1.531)
Postpartum hemorrhage, n (%)	16 (8.6 %)	19 (17.5 %)	0.723	0.842 (0.447–1.586)
Cesarean delivery, n (%)	92 (49.7 %)	44 (23.8 %)	<0.001	2.091 (1.555–2.811)
Meconium-stained amniotic fluid, n (%)	21 (11.4 %)	28 (24.5 %)	0.358	0.750 (0.442–1.271)
Adherent placenta, n (%)	5 (2.7 %)	17 (9.2 %)	0.014	3.401 (1.280–9.009)
Anemia at the 1st trimester, n (%)	12 (6.5 %)	4 (2.2 %)	0.071	3.000 (0.986–9.131)
Anemia at the 2nd trimester, n (%)	38 (20.5 %)	9 (4.9 %)	<0.001	4.222 (2.102–8.481)
Anemia at the 3rd trimester, n (%)	78 (42.2 %)	38 (20.5 %)	<0.001	2.053 (1.476–2.855)

thalassemia characteristics. Significant differences were observed in the incidence rates of HDP, cesarean delivery, adherent placenta, anemia in the 2nd trimester, and anemia in the 3rd trimester when comparing the three groups. Conversely, no statistically significant differences were found among the three groups regarding the incidence rates of GDM, preeclampsia, eclampsia, ICP, placental abruption, hydramnios, oligohydramnios, PROM, chorioamnionitis, postpartum hemorrhage, meconium-stained amniotic fluid, or anemia in the 1st trimester.

Comparisons of the obstetric outcomes between the sub groups α-thalassemia and β-thalassemia with control group

Table 4 presents the subgroup analysis among different types of thalassemia traits for significant obstetric outcomes. Significant differences were observed between the α-thalassemia trait group and the control group in the rates of GDM, HDP, cesarean delivery, anemia in the 2nd trimester, and anemia in the 3rd trimester, with RR and 95 % CI of 2.252 (1.073–4.729),

Table 3: Comparisons of the obstetric outcomes between the sub groups.

Outcomes	*α*-thalassemia (n=112)	β-thalassemia (n=73)	Control group (n=185)	p-Value
GDM, n (%)	15 (13.4 %)[a]	9 (12.3 %)	11 (5.9 %)	0.056
HDP, n (%)	6 (5.4 %)[a]	3 (4.1 %)	1 (0.5 %)	0.018
Preeclampsia, n (%)	4 (3.6 %)	0 (0 %)	1 (0.5 %)	0.073
Eclampsia, n (%)	1 (0.9 %)	1.1.4 (%)	0 (0 %)	0.249
ICP, n (%)	2 (1.8 %)	2 (2.7 %)	3 (1.6 %)	0.782
Placental abruption, n (%)	6 (5.4 %)	0 (0 %)	4 (2.2 %)	0.091
Hydramnios, n (%)	0 (0 %)	1 (1.4 %)	2 (1.1 %)	0.592
Oligohydramnios, n (%)	8 (7.1 %)	5 (6.8 %)	10 (5.4 %)	0.811
PROM, n (%)	24 (21.4 %)	11 (15.1 %)	50 (27.0 %)	0.116
Chorioamnionitis, n (%)	15 (15.2 %)	13 (17.8 %)	31 (16.8 %)	0.867
Postpartum hemorrhage, n (%)	7 (6.3 %)	9 (12.3 %)	19 (10.3 %)	0.315
Cesarean delivery, n (%)	58 (51.8 %)[a]	34 (46.6 %)[b]	44 (23.8 %)	<0.0001
Meconium-stained amniotic fluid, n (%)	11 (9.8 %)	10 (13.7 %)	28 (15.1 %)	0.433
Adherent placenta, n (%)	1 (0.9 %)[a]	4 (5.5 %)	17 (9.2 %)	0.006
Anemia at the 1st trimester, n (%)	8 (7.1 %)	4 (5.5 %)	4 (2.2 %)	0.103
Anemia at the 2nd trimester, n (%)	17 (15.2 %)[a]	21 (28.8 %)[b]	9 (4.9 %)	<0.0001
Anemia at the 3rd trimester, n (%)	40 (35.7 %)[a]	38 (52.1 %)[b]	38 (20.5 %)	<0.0001

[a]Indicates comparison between the α-thalassemia trait pregnant women group and the control group pregnant women group, p<0.05; [b]indicates comparison between the β-thalassemia trait pregnant women group and the control group pregnant women group, p<0.05.

Table 4: Comparisons of the obstetric outcomes between the sub groups α-thalassemia and β-thalassemia with control group.

Outcomes	α-thalassemia (n=112) RR (95 % CI)	β-thalassemia (n=73) RR (95 % CI)
GDM, n (%)	2.252 (1.073–4.729)[a]	2.073 (0.897–4.795)
HDP, n (%)	9.911 (1.209–81.254)[a]	7.603 (0.804–71.909)
Preeclampsia, n (%)	6.607 (0.748–58.373)	–
Eclampsia, n, %	–	–
ICP, n (%)	1.101 (0.187–6.489)	1.689 (0.288–9.905)
Placental abruption, n (%)	2.478 (0.715–8.589)	–
Hydramnios, n (%)	–	1.267 (0.117–13.761)
Oligohydramnios, n (%)	1.321 (0.537–3.249)	1.267 (0.448–3.581)
PROM, n (%)	0.793 (0.518–1.214)	0.558 (0.308–1.010)
Chorioamnionitis, n (%)	0.906 (0.526–1.559)	1.063 (0.590–1.914)
Postpartum hemorrhage, n (%)	0.609 (0.264–1.401)	1.2 (0.570–2.530)
Cesarean delivery, n (%)	2.177 (1.591–2.980)[a]	1.958 (1.371–2.796)[b]
Meconium-stained amniotic fluid, n (%)	0.649 (0.336–1.251)	0.905 (0.463–1.768)
Adherent placenta, n (%)	0.097 (0.013–0.720)[a]	0.596 (0.208–1.712)
Anemia at the 1st trimester, n (%)	3.304 (1.018–10.720)	2.534 (0.651–9.866)
Anemia at the 2nd trimester, n (%)	3.120 (1.440–6.760)[a]	5.913 (2.843–12.300)[b]
Anemia at the 3rd trimester, n (%)	1.739 (1.193–2.535)[a]	2.534 (1.770–3.628)[b]

[a]Indicates comparison between the α-thalassemia trait pregnant women group and the control group, $p<0.05$; [b]indicates comparison between the β-thalassemia trait pregnant women group and the control group, $p<0.05$.

9.911 (1.209–81.254), 2.177 (1.591–2.980), 0.097 (0.013–0.720), 3.120 (1.440–6.760), and 1.739 (1.193–2.535), respectively. In contrast, comparing the β-thalassemia group with the control group revealed significant differences in the rates of cesarean delivery, anemia in the 2nd trimester, and anemia in the 3rd trimester, with RR and 95 % CI of 1.958 (1.371–2.796), 5.913 (2.843–12.300), and 2.534 (1.770–3.628), respectively.

Comparisons of obstetric outcomes between the α-thalassemia trait and β-thalassemia trait

Table 5 indicates significant differences between α-thalassemia trait and β-thalassemia groups in the anemia rates of the 2nd trimester and 3rd trimester, with RR and 95 % CI of 1.894 (1.074–3.344) and 1.458 (1.046–2.033), respectively. However, there were no statistically significant differences observed between the two groups in the rates of GDM, HDP, cesarean delivery, and adherent placenta, with RR and 95 % CI of 1.086 (0.502–2.351), 1.304 (0.337–5.050), 1.112 (0.821–1.507), and 0.163 (0.019–1.429), respectively.

Comparison of neonatal outcomes between thalassemia traits and control group of pregnant women

Following the exclusion of five cases of stillbirth and four cases of fetal malformation in both the thalassemia trait group and control group, neonatal outcomes were analyzed and are presented in Table 6. No statistically significant differences were found between the study and control groups in the rates of preterm birth, low birth weight, macrosomia, IUGR, neonatal asphyxia, fetal distress, fetal malformation, or stillbirth.

Comparisons of the neonatal outcomes between the sub groups α-thalassemia trait, β-thalassemia trait and control group

Table 7 presents the subgroup analysis among different types of thalassemia traits for neonatal outcomes. Statistically significant differences were observed in the incidence rates of low birth weight and fetal malformation among the three groups. However, no statistically significant differences were found in the incidence rates of preterm birth, macrosomia, IUGR, neonatal asphyxia, fetal distress, and stillbirth.

Comparisons of neonatal outcomes between α-thalassemia and β-thalassemia with control group

Table 8 presents the subgroup analysis among different types of thalassemia traits for neonatal outcomes. Significant

Table 5: Comparisons of obstetric outcomes between the α-thalassemia and β-thalassemia.

Outcomes	α-thalassemia (n=112)	β-thalassemia (n=73)	p-Value	Relative risk (95 % CI)
GDM, n (%)	15 (13.4 %)	9 (12.3 %)	1.000	1.086 (0.502–2.351)
HDP, n (%)	6 (5.4 %)	3 (4.1 %)	1.000	1.304 (0.337–5.050)
Cesarean delivery, n (%)	58 (51.8 %)	34 (46.6 %)	0.548	1.112 (0.821–1.507)
Adherent placenta, n (%)	1 (0.9 %)	4 (5.5 %)	0.080	0.163 (0.019–1.429)
Anemia at the 2nd trimester, n (%)	17 (15.2 %)	21 (28.5 %)	0.040	1.894 (1.074–3.344)
Anemia at the 3rd trimester, n (%)	40 (35.7 %)	38 (52.1 %)	0.033	1.458 (1.046–2.033)

Table 6: Comparisons of neonatal outcomes between the two groups.

Outcomes	Study group (n=185)	Control group (n=185)	p-Value	Relative risk (95 % CI)
Preterm birth, n (%)	16 (8.6 %)	10 (5.4 %)	0.309	1.600 (0.746–3.433)
Low birth weight, n (%)	14 (7.6 %)	7 (3.8 %)	0.176	2.000 (0.826–4.842)
Macrosomia, n (%)	3 (1.6 %)	4 (2.2 %)	1.000	0.750 (0.170–3.305)
IUGR, n (%)	4 (2.2 %)	2 (1.1 %)	0.685	2.000 (0.371–10.786)
Fetal distress, n (%)	18 (9.7 %)	16 (8.6 %)	0.857	1.125 (0.592–2.137)
Neonatal asphyxia, n (%)	5 (2.7 %)	6 (3.2 %)	1.000	0.833 (0.259–2.683)
Fetal malformation, n (%)	4 (2.2 %)	0 (0 %)	0.123	–
Stillbirth, n (%)	4 (2.2 %)	1 (0.5 %)	0.372	4.000 (0.451–35.449)

Table 7: Comparisons of neonatal outcomes between the α-thalassemia, β-thalassemia and control group.

Outcomes	α-thalassemia (n=112)	β-thalassemia (n=73)	Control group (n=185)	p-Value
Preterm birth, n (%)	11 (9.8 %)	5 (6.8 %)	10 (5.4 %)	0.361
Low birth weight, n (%)	12 (10.7 %)[a]	2 (2.7 %)	7 (3.8 %)	0.034
Macrosomia, n (%)	2 (1.8 %)	1 (1.4 %)	4 (2.2 %)	1.000
IUGR, n (%)	3 (2.7 %)	1 (1.4 %)	2 (1.1 %)	0.574
Fetal distress, n (%)	10 (8.9 %)	8 (11.0 %)	16 (8.6 %)	0.839
Neonatal asphyxia, n (%)	3 (2.7 %)	2 (2.7 %)	6 (3.2 %)	1.000
Fetal malformation, n (%)	4 (3.6 %)[a]	0 (0 %)	0 (0 %)	0.010
Stillbirth, n (%)	1 (0.9 %)	3 (4.1 %)	1.05 (%)	0.096

[a]Indicates comparison between the α-thalassemia trait pregnant women group and the control group, p<0.05.

Table 8: Comparisons of neonatal outcomes between α-thalassemia and β-thalassemia with control group.

Outcomes	α-thalassemia (n=112) vs. control group (n=185)	β-thalassemia (n=73) vs. control group (n=185)	α-thalassemia (n=112) vs. β-thalassemia (n=73)
Preterm birth, n (%)	1.817 (0.797–4.140)	1.267 (0.448–3.581)	–
Low birth weight, n (%)	2.832 (1.149–6.980)[a]	0.724 (0.154–3.404)	3.911 (0.901–16.968)
Macrosomia, n (%)	0.826 (0.154–4.436)	0.634 (0.073–5.574)	1.304 (0.120–14.117)
IUGR, n (%)	2.478 (0.420–14.601)	1.267 (0.117–13.761)	1.955 (0.207–18.439)
Fetal distress, n (%)	1.032 (0.485–2.195)	1.267 (0.567–2.832)	0.815 (0.337–1.968)
Neonatal asphyxia, n (%)	0.826 (0.211–3.237)	0.845 (0.174–4.090)	0.978 (0.167–8.710)
Fetal malformation, n (%)	–[a]	–	–
Stillbirth, n (%)	1.652 (0.104–26.146)	7.603 (0.804–71.909)	0.217 (0.023–2.049)

[a]Indicates comparison between the α-thalassemia trait pregnant women group and the control group, p<0.05.

differences were observed between the α-thalassemia group and the control group in the rate of low birth weight, with an RR and 95 % CI of 2.832 (1.149–6.980).

Comparisons of hematological indicators between thalassemia traits and control group

Table 9 presents comparisons of hematological indicators between the thalassemia trait and control groups. Significant differences were found in Hb, MCV, MCH, and RDW levels between the two groups during the 1st, 2nd, and 3rd trimesters. On the other hand Table 10 presents significant differences of Hb, MCH, and RDW levels and no statistically significant differences of MCV levels during the 1st, 2nd, and 3rd trimesters for the thalassemia trait.

Discussion

The effect of thalassemia traits on hematological indices during pregnancy

Patients with thalassemia traits typically do not exhibit clinical symptoms; however, they are susceptible to develop

Table 9: Comparisons of hematological indicators between the two groups during the 1st trimester, 2nd trimester and 3rd trimester.

Variables	Trimester	Study group (n=185)	Control group (n=185)	p-Value
Hb, g/L, $\bar{x}$ ±SD	1st	126.74 ± 11.61	134.51 ± 11.59	<0.001
	2nd	114.87 ± 13.77	123.45 ± 10.11	<0.001
	3rd	111.89 ± 14.31	127.09 ± 10.72	<0.001
MCV, fL, $\bar{x}$ ±SD	1st	81.58 ± 7.05	89.59 ± 4.99	<0.001
	2nd	81.18 ± 7.70	92.42 ± 4.90	<0.001
	3rd	81.04 ± 7.58	92.42 ± 5.13	<0.001
MCH, pg, $\bar{x}$ ±SD	1st	26.97 ± 2.80	30.42 ± 1.99	<0.001
	2nd	26.32 ± 2.99	30.91 ± 1.97	<0.001
	3rd	26.16 ± 2.98	32.47 ± 1.65	<0.001
RDW, %, $\bar{x}$ ±SD	1st	14.30 ± 1.78	13.38 ± 1.91	<0.001
	2nd	14.97 ± 1.85	13.69 ± 1.11	<0.001
	3rd	15.22 ± 1.85	13.99 ± 1.51	<0.001

more severe anemia during pregnancy, posing risks to maternal and fetal health [27]. Pregnant women with thalassemia constitute a distinct group requiring ongoing monitoring of routine blood tests from early pregnancy stages to assess maternal and fetal risks. Monitoring parameters like Hb, MCV, MCH, and RDW is crucial for indicating anemia [28]. Thalassemia-associated anemia is characterized by microcytic hypochromic morphology, typically presenting with lower levels of Hb, MCH, and MCV, and elevated or increasing RDW [29, 30]. This study revealed that pregnant women with thalassemia traits experience significant declining levels of Hb, MCV, and MCH, alongside increasing RDW as pregnancy progresses, underscoring their association with pregnancy outcomes and emphasizing the importance of early discovery in this population. Liang et al. similarly reported lower Hb, MCV, and MCH, and higher RDW in pregnant women carrying the thalassemia gene, which is consistent with our findings [31]. Numerous domestic and international studies have highlighted the adverse effect of thalassemia on pregnancy [28, 32–35]. Genetic mutations associated with thalassemia disrupt globin synthesis, commonly leading to microcytic hypochromic anemia. Therefore, assessing Hb, MCV, MCH, and RDW levels in pregnant women has become pivotal for screening thalassemia, providing valuable diagnostic insights and guiding subsequent management and delivery decisions [36]. Furthermore, this study advocates for the routine measurement of Hb, MCV, MCH, and RDW levels as a straightforward method to screen pregnant women for thalassemia trait.

The effect of thalassemia trait on neonatal outcomes

The effect of thalassemia trait on the incidence of neonatal asphyxia

Neonatal asphyxia refers to the inability of the newborn to initiate breathing at birth, often caused by complications during delivery [37]. However, the study found no statistically significant difference in the incidence of neonatal asphyxia between the thalassemia trait group and the control group. Sheiner et al. reported a significant increase in the rate of neonatal asphyxia with increasing severity of maternal anemia [38]. Considering that pregnant women with thalassemia traits rarely experience moderate to severe anemia, it may be the reason why there is minimal adverse effect on fetal outcomes.

The effect of thalassemia trait on low birth weight in newborns

A newborn's birth weight serves as a key indicator for assessing neonatal health and assessing the effectiveness of prenatal care. It not only reflects intrauterine nutrition and fetal growth during pregnancy but also plays a key role in determining future physical and cognitive development [39, 40]. Throughout pregnancy, numerous factors influence fetal weight, including maternal nutritional intake, placental function in nutrient transport, maternal oxygen-carrying capacity, and the genetic potential of the fetus. In cases of mild anemia during pregnancy, the mother and the fetus' bone marrow both compete for serum iron (Fe). Since Fe is transported from the mother to the fetus through the placenta in a unidirectional manner, fetal tissues have a preferential uptake of Fe, thereby mitigating severe fetal Fe

Table 10: Comparisons of hematological indicators of study group (n=185) during the 1st trimester, 2nd trimester and 3rd trimester.

Variables	Trimester 1st	Trimester 2nd	Trimester 3rd	p-Value
Hb, g/L, $\bar{x}$ ±SD	126.74 ± 11.61	114.87 ± 13.77	111.89 ± 14.31	<0.001
MCV, fL, $\bar{x}$ ±SD	81.58 ± 7.05	81.18 ± 7.70	81.04 ± 7.58	0.769
MCH, pg, $\bar{x}$ ±SD	26.97 ± 2.80	26.32 ± 2.99	26.16 ± 2.98	0.020
RDW, %, $\bar{x}$ ±SD	14.30 ± 1.78	14.97 ± 1.85	15.22 ± 1.85	<0.001

deficiency. However, moderate to severe maternal anemia compromises the placental delivery of oxygen and nutrients to the fetus, potentially leading to fetal growth restriction, fetal distress, preterm birth, or stillbirth [41].

Studies have identified gestational age as the foremost determinant of newborn birth weight, followed by factors like fetal number, gender, maternal education level, maternal age, maternal nutritional status, residential location, parity, and obstetric history [42, 43]. Some authors argue that thalassemia affects newborn birth weight and poses a risk factor for low birth weight [44, 45]. This is attributed to reduced hemoglobin levels in pregnant women with thalassemia, which diminishes nutrient transfer to the fetus through the placenta, thereby affecting newborn birth weight. The results of this study found a lower incidence of low birth weight in the thalassemia trait group compared to the control group, although this difference was not statistically significant. However, subgroup analysis indicated a statistically significant increase in low birth weight incidence in α-thalassemia trait, while no significant difference was found in β-thalassemia trait compared to the control group, consistent with the findings of Pang et al. [46]. Conversely, a systematic review in China proposed that α-thalassemia is not associated with increased risk of low birth weight in newborns, whereas β-thalassemia is a significant risk factor, conflicting with the conclusions of our study [47]. This inconsistency may be influenced by regional dietary habits; variations in dietary practices can effect maternal nutrition and subsequently affect fetal intrauterine development, contributing to regional disparities in research outcomes.

The effect of thalassemia trait on maternal outcomes

The effect of thalassemia trait on anemia in pregnant women

In pregnant women with thalassemia, genetic mutations impair globin chain synthesis due to α or β gene deficiencies, resulting in ineffective red blood cell production. Additionally, the influence of human chorionic gonadotropin (HCG) exacerbates hemolytic anemia, intensifying the severity of thalassemia during pregnancy when compared to normal pregnancies. Patients with thalassemia trait often exhibit no obvious symptoms due to compensatory effects from unaffected genes, and their hemoglobin levels may appear normal. However, during illness or pregnancy, these compensatory mechanisms are limited and anemia symptoms and its related complications can manifest [48]. Research indicates that physiological changes leading to anemia during pregnancy may exacerbate anemia in pregnant women with thalassemia trait, adversely affecting maternal and fetal health and potentially leading to long-term effects on newborns [49]. Our study found an RR and 95 % CI of 3.000 (0.986–9.131) in the incidence of anemia between the thalassemia trait and control groups in early pregnancy, which slightly failed to reach statistical significance. However, significant differences were observed in the incidence of anemia between the two groups during mid and late pregnancy. Subgroup analysis further indicated significantly higher incidence of anemia in the β-thalassemia trait group compared to the α-thalassemia trait group during mid and late pregnancy. Li et al. similarly reported significantly lower Hb levels in late pregnancy among women with thalassemia trait compared to those without, which is consistent with our findings [50]. Without appropriate interventions, the prevalence of anemia among pregnant women with thalassemia trait is likely to escalate as pregnancy progresses.

The effect of thalassemia trait on gestational diabetes mellitus

The occurrence of GDM is associated with changes in the endocrine environment during pregnancy. As blood volume increases, pregnant women often experience relatively insufficient insulin secretion. In early pregnancy, maternal blood glucose levels tend to decrease with advancing gestational age. However, in mid and late pregnancy, the levels of anti-insulin substances like progesterone and estrogen, increase, reducing insulin sensitivity. This reduction in insulin sensitivity leads to insufficient insulin secretion to meet the physiological demands of pregnancy, resulting in abnormal glucose metabolism [49, 50].

There are both domestic and international controversies regarding thalassemia and whether it adversely affects pregnancy outcomes. The results of this study indicate that pregnant women with thalassemia trait are more likely to develop GDM compared to normal pregnant women, similar to the findings of Gérardin et al. [51]. Furthermore, the subgroup analysis in this study revealed a statistically significant difference between pregnant women with α-thalassemia and normal pregnant women, which is consistent with the study by Lao and Ho [52]. However, no statistically significant difference was found between pregnant women with β-thalassemia and normal pregnant women, aligning with the results reported by Tsatalas et al. [53]. Some literature reports indicate that the occurrence of GDM in pregnant women with thalassemia trait is not statistically significant compared to normal pregnant women [54, 55]. This discrepancy may result because these studies do not differentiate between types of thalassemia

gene mutations, indicating that the differences in results might be related to the diversity of thalassemia types. Additionally, variations in lifestyle and dietary habits among pregnant women could also contribute to these differing outcomes.

The effect of thalassemia traits on hypertensive disorders of pregnancy, preeclampsia, and eclampsia

HDP are a group of complications commonly seen during pregnancy and are a major cause of morbidity and mortality in pregnant women and newborns, accounting for 25 % of maternal deaths [56–58]. The global incidence of HDP is between 8 and 10 % [59]. HDP can be classified based on severity into mild, moderate, and severe forms. Severe HDP, also known as pre-eclampsia and eclampsia, is characterized by convulsions on the basis of hypertension, with severe pre-eclampsia accounting for about 39.96 % of cases [60]. Pregnancy complicated by thalassemia can lead to an increased risk of adverse pregnancy outcomes like fetal growth restriction, preterm birth, and even fetal death *in utero*, and may cause serious complications such as thromboembolism, cardiac abnormalities, and endocrine dysfunction [61]. Therefore, pregnancies complicated by thalassemia require proactive and effective prenatal screening and diagnosis along with routine prenatal examinations [62]. The results of this study, similar to those published by Luo et al., demonstrate that the incidence of HDP in pregnant women with thalassemia trait is significantly higher than in the normal pregnant group [63]. However, this study also reveals that the incidence of preeclampsia and eclampsia in pregnant women with thalassemia trait is not statistically different from that in normal pregnant women, which is consistent with the findings of Zhang et al. [64]. Some international studies have revealed that the incidence of preeclampsia in pregnant women with thalassemia trait is higher than in normal pregnant women. This difference may be related to the proportion of primiparas in the thalassemia group and may also be influenced by dietary, environmental, social, psychological, genetic, and economic factors [65]. Clinical calcium deficiency has been commonly considered a major inducer of HDP [66].

The effect of thalassemia traits on the mode of delivery

The decision for a cesarean section involves many confounding factors like advanced maternal age, multiple pregnancies, primiparity, abnormal fetal position, and fetal birth weight [67, 68]. Consequently, whether thalassemia increases the risk of cesarean section remains controversial. A systematic review by Lai et al. on the relationship between thalassemia and pregnancy outcomes indicated that β-thalassemia is a risk factor for cesarean section [17]. This may be due to anemia during pregnancy increasing the incidence of fetal distress *in utero*, thereby raising the cesarean section rate. However, α-thalassemia is not a risk factor for cesarean section in pregnant women. The review proposes a weak correlation between thalassemia and cesarean section, potentially due to an increased incidence of fetal distress *in utero* caused by anemia during pregnancy, which leads to a higher rate of cesarean sections. Moreover, this meta-analysis indicated that the cesarean section rate in the thalassemia group was higher than in the normal group [31]. According to Zhu et al., the cesarean section rate in women with thalassemia was significantly higher than that in non-thalassemic women, attributing this to the increased incidence of fetal distress *in utero* due to anemia during pregnancy [69]. The results of this study revealed that the cesarean section rate in the thalassemia trait group was significantly higher than in the normal pregnant women group, aligning with previous studies [47, 63, 69–73]. Furthermore, this study revealed no statistically significant difference in the incidence of fetal distress *in utero* between the thalassemia trait and normal pregnant women groups. Previous studies have indicated that patients with thalassemia trait during pregnancy have reduced body defense capabilities, decreased tolerance to vaginal delivery and cesarean section, and are prone to hemorrhagic shock, neonatal asphyxia, and restricted fetal growth, which differs from the findings of this study [74, 75]. This study indicates that pregnant women with thalassemia, when combined with other diseases during pregnancy, experience an increased incidence of fetal distress *in utero* and adverse fetal events, thereby raising the cesarean section rate.

The other effect of thalassemia traits on adverse pregnancy outcomes

Thalassemia is a chronic hereditary hemolytic disease resulting from the deletion or mutation of globin genes, leading to a globin synthesis disorder. It is also known as globin regeneration disorder anemia. Anemia, a high-risk factor during pregnancy, can increase pregnancy risks even in its mild form. In severe cases, it may lead to a reduction in effective circulating blood volume in the uterus, causing miscarriage, preterm birth, or fetal death due to ischemia and hypoxia. Research by Sheiner et al. demonstrated that pregnant women with mild β-thalassemia have a higher incidence of IUGR and oligohydramnios compared to non-thalassemic pregnant women [38]. However, there is no significant difference in the incidence of congenital malformations or perinatal death. Studies conducted by Wang et al. and Pang et al. indicated that thalassemia trait significantly increases

the incidence of preterm birth and adverse postpartum pregnancy outcomes [47, 76]. Yang et al. revealed that chronic anemia combined with pregnancy can affect pregnancy outcomes, increasing the likelihood of preterm birth and postpartum hemorrhage [77]. Conversely, the study conducted by Zhang et al. found no statistically significant differences between thalassemia pregnant women and normal pregnant women in terms of macrosomia, polyhydramnios, oligohydramnios, or postpartum hemorrhage. Research by Chen et al. and Guo et al. demonstrated that patients with thalassemia trait exhibit weakened bodily defense capabilities, decreased tolerance to both vaginal delivery and cesarean section, and an increased susceptibility to hemorrhagic shock, neonatal asphyxia, and restricted fetal growth [74, 75]. Farmaki et al. further revealed that thalassemia gene carriers are at risk for late-term fetal death or neonatal death due to genetic deletions, underscoring the importance of SEA gene screening for pregnant women [78]. This study did not find statistically significant differences in maternal and perinatal outcomes, including ICP, placental abruption, hydramnios, oligohydramnios, premature rupture of membranes (PROM), chorioamnionitis, postpartum hemorrhage, meconium-stained amniotic fluid, adherent placenta, preterm birth, macrosomia, IUGR, fetal malformation, and stillbirth between the thalassemia trait and control groups. However, subgroup analysis revealed that the incidence of fetal malformation in pregnant women with α-thalassemia trait was significantly higher than in normal pregnant women. In contrast, the incidence in pregnant women with β-thalassemia trait was not statistically significant compared to normal pregnant women.

Limitations

This study has certain limitations. Firstly, as a retrospective study utilizing data from hospital electronic medical records, it lacks information on the dietary habits of the pregnant women involved. Variations in diet, cultural customs, and iron intake can influence pregnancy outcomes and may introduce regional differences in findings. Furthermore, the limited sample size may introduce bias, impacting the generalizability and accuracy of the results. Future studies with larger sample sizes and prospective data collection are recommended to validate these findings across diverse populations.

Conclusions

This study presents novel findings on the hematological changes during pregnancy, demonstrating that as pregnancy progresses, levels of Hb, MCV, and MCH decline, while RDW increases. Thalassemia traits significantly impact of on the development of anemia, particularly in the second and third trimesters, with β-thalassemia traits exhibiting a more pronounced effect compared to α-thalassemia traits. Furthermore, this study identifies thalassemia traits, especially α-thalassemia, as critical contributors to pregnancy complications such as GDM, HDP, and increased rates of cesarean deliveries. Notably, α-thalassemia trait emerges as a potential risk factor for low birth weight and fetal malformations, underscoring the need for careful monitoring and management of pregnant individuals with these traits. These findings contribute to a better understanding of how thalassemia traits influence maternal and fetal health outcomes and provide valuable insights for clinical practice and prenatal care.

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