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# THE ASSOCIATION OF LOW HEMOGLOBIN WITH THE RISK OF ADVERSE FETOMATERNAL OUTCOMES IN PATIENTS OF THALASSEMIA MINOR - A COHORT STUDY

*Original Research*

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**Acknowledgement:** The authors thank the patients and staff of Gynae C Unit, MTI-KTH Peshawar, for their cooperation.

Conflict of Interest: None

Grant Support & Financial Support: None

## ABSTRACT

**Background:** Beta-thalassemia minor is generally considered a benign carrier state; however, emerging evidence suggests it may be associated with adverse maternal and neonatal outcomes, especially when compounded by anemia during pregnancy. Understanding this relationship is crucial for developing targeted antenatal care strategies in regions where thalassemia is prevalent.

**Objective:** To determine the association of low hemoglobin levels with the risk of adverse feto-maternal outcomes in pregnant women diagnosed with beta-thalassemia minor.

**Methods:** A prospective cohort study was conducted at Gynae C Unit, MTI-KTH Peshawar, over six months. A total of 158 pregnant women were enrolled, equally divided into exposed (beta-thalassemia minor with low Hb) and non-exposed (without thalassemia, normal Hb) groups using non-probability consecutive sampling. Data on demographics, hemoglobin levels, obstetric history, and adverse outcomes were recorded. Outcomes assessed included preterm birth, low birth weight, neonatal anemia, IUGR, maternal anemia, need for blood transfusion, and oligohydramnios. Data were analyzed using SPSS v23.0; relative risk (RR) and Chi-square tests were applied, with $p < 0.05$ considered statistically significant.

**Results:** Adverse outcomes were significantly more frequent in the exposed group. Preterm birth (24.1% vs. 10.1%), low birth weight (32.9% vs. 15.2%), neonatal anemia (26.6% vs. 11.4%), IUGR (21.5% vs. 8.9%), and maternal anemia (48.1% vs. 17.7%) were all more prevalent among women with beta-thalassemia minor. Blood transfusion and oligohydramnios were also notably higher in the exposed group.

**Conclusion:** Beta-thalassemia minor with low hemoglobin is significantly associated with adverse feto-maternal outcomes. These findings highlight the need for early screening and enhanced antenatal surveillance in affected pregnancies to mitigate risks.

**Keywords:** Anemia, Beta-Thalassemia, Fetal Growth Retardation, Hemoglobinopathies, Neonatal Outcomes, Obstetric Complications, Pregnancy, Pregnancy Outcome.

## INTRODUCTION

Thalassemias are a group of inherited hematological disorders characterized by the reduced or absent synthesis of one or more globin chains, most commonly the alpha or beta chains of hemoglobin. Hemoglobin, the oxygen-carrying protein within red blood cells, is composed of two alpha and two beta chains. Deficiency in either chain disrupts the formation of functional hemoglobin, resulting in microcytic anemia and impaired oxygen transport from early childhood throughout life. Thalassemia follows an autosomal recessive inheritance pattern, requiring both parents to be carriers or affected for the disease to manifest in offspring. Mutations or deletions in the globin gene clusters underlie the disease, with over 200 mutations identified to date (1-3). Alpha thalassemia typically results from gene deletions affecting the alpha-globin genes and is more prevalent among populations in Asia and Africa. In contrast, beta-thalassemia is primarily caused by point mutations, especially in splice sites and promoter regions of the beta-globin gene on chromosome 11, and is more common in individuals from the Mediterranean, Southeast Asia, and parts of Africa (4,5). In these regions, the carrier frequency may be as high as 10%. In the United States, precise epidemiological data remain limited due to the lack of comprehensive screening programs (6,7). Beta-thalassemia minor, or trait, is the heterozygous state of the disease and is generally associated with mild anemia, reduced mean corpuscular volume and hemoglobin, and elevated levels of hemoglobin A2 and/or fetal hemoglobin. Though often clinically silent, beta-thalassemia minor may unmask during pregnancy, particularly in the second and third trimesters, where physiological hemodilution exaggerates anemia (8,9). A case-control study demonstrated that maternal anemia was significantly more prevalent among beta-thalassemia minor cases (45.2%) compared to controls (2.1%), suggesting a need for greater vigilance in these pregnancies (10,11).

Inadequate globin synthesis not only compromises oxygen delivery to maternal and fetal tissues but also increases maternal vulnerability to complications such as cardiomyopathy and diabetes due to iron overload, especially in more severe thalassemia syndromes. These risks necessitate closer clinical monitoring and individualized management to prevent adverse outcomes (12). In beta-thalassemia major (TM) and intermedia (TI), pregnancies are often complicated by higher transfusion needs, with TM cases showing significant increases in red cell requirements and 70% of TI cases requiring transfusion support. Despite these complications, studies report no significant differences in stillbirth, small for gestational age neonates, or preterm birth between TM and TI pregnancies (13,14). While considerable research has focused on severe forms of thalassemia, there remains a lack of clarity regarding the specific maternal and neonatal outcomes associated with beta-thalassemia minor. Despite its relatively high prevalence, particularly in certain ethnic populations, the relationship between low hemoglobin levels and adverse feto-maternal outcomes in this group remains underexplored. This gap in evidence is especially significant in resource-limited settings where targeted antenatal care can influence outcomes. Understanding this association is essential to inform guidelines, ensure timely interventions, and improve maternal and neonatal prognosis. Therefore, this study aims to determine the association of low hemoglobin with the risk of adverse feto-maternal outcomes in patients diagnosed with beta-thalassemia minor.

## METHODS

A cohort study was conducted at Gynae C Unit, MTI-KTH Peshawar over a duration of six months following approval of the synopsis. Ethical clearance was obtained from the Institutional Review Board and CPSP Karachi prior to the initiation of data collection. Written informed consent was obtained from all participants after providing them with a complete explanation of the study objectives, procedures, and potential risks and benefits. Patient confidentiality was maintained throughout the study, and all data were collected and handled solely by the principal investigator under the supervision of a consultant hematologist and gynecologist, each with a minimum of three years of post-fellowship experience. The sample size was calculated using the WHO formula, with assumptions based on a caesarean section rate of 83.9% in the exposed group and 67% in the non-exposed group (11), with 95% confidence interval, 80% power, and 5% margin of error, resulting in a total of 158 participants—79 in each group. A non-probability consecutive sampling technique was employed to recruit participants. Participants included pregnant women between 20 and 40 years of age, presenting with a gestational age of 20 weeks confirmed by last menstrual period (LMP). The exposed group comprised women diagnosed with beta-thalassemia minor and low hemoglobin levels, while the non-exposed group included women with normal hemoglobin levels and no diagnosis of beta-thalassemia minor. Diagnosis of beta-thalassemia minor was confirmed through complete blood count (CBC),

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NESTROF screening, and hemoglobin electrophoresis showing elevated HbA2 levels (≥3.5%). Exclusion criteria were patients with a history of recurrent spontaneous abortions (two or more consecutive losses), previous pregnancies complicated by neural tube defects, history of infertility, or any known chronic medical condition that could confound pregnancy outcomes (15,16).

Data collection involved a detailed clinical assessment including obstetric, menstrual, and family histories. Hematological testing and sonographic evaluation were performed where indicated. Participants were followed until delivery, and outcomes were recorded for both mother and neonate. The adverse feto-maternal outcomes assessed included preterm birth, low birth weight, neonatal anemia, intrauterine growth restriction (IUGR), maternal anemia, need for blood transfusions, and oligohydramnios. Data were entered and analyzed using SPSS version 23.0. Numerical variables such as age, body mass index (BMI), hemoglobin levels, and gestational age were described using means with standard deviations or medians with interquartile ranges, based on normality determined via the Shapiro-Wilk test. Categorical variables, including age groups, social class, residence, educational status, occupational status, and consanguinity, were summarized using frequencies and percentages. Relative risk (RR) was calculated to assess the strength of association between low hemoglobin levels and adverse feto-maternal outcomes. An RR > 1 was interpreted as a positive association. Stratification was performed for potential effect modifiers such as age, social class, consanguineous marriage, and BMI. Post-stratification analysis using Chi-square test or Fisher's exact test was applied, with a p-value of $<0.05$ considered statistically significant. Results were displayed using tables and graphical representations for clarity and comprehensive reporting.

## RESULTS

The study cohort consisted of 158 pregnant women, equally divided between the exposed group (beta-thalassemia minor with low hemoglobin levels) and the non-exposed group (without thalassemia and with normal hemoglobin levels). The mean age of participants in the exposed group was 28.6 ± 4.5 years, while the non-exposed group had a mean age of 29.2 ± 4.2 years. Mean hemoglobin levels were 9.1 ± 0.7 g/dL and 11.3 ± 0.6 g/dL in the exposed and non-exposed groups, respectively. The average BMI was slightly lower in the exposed group (24.8 ± 2.3 kg/m²) compared to the non-exposed group (25.1 ± 2.0 kg/m²). In terms of socioeconomic distribution, 48.1% of the exposed group were from lower socioeconomic backgrounds, while 34.2% belonged to the middle class. In contrast, the non-exposed group had a more even distribution, with 34.2% from middle and 22.8% from upper socioeconomic classes. Regarding employment status, 72.2% of the exposed group were unemployed compared to 67.1% in the non-exposed group. Rural residence was reported by 62% of the exposed participants, whereas 53.2% of the non-exposed group lived in rural areas. Educational attainment was similar in both groups, with the majority completing at least middle or higher education. Consanguinity was more common among the exposed group (57%) compared to the non-exposed group (40.5%). Assessment of adverse feto-maternal outcomes revealed a notably higher burden in the exposed group. Preterm birth occurred in 24.1% of exposed participants versus 10.1% in the non-exposed group. Similarly, low birth weight was observed in 32.9% of the exposed group compared to 15.2% of the non-exposed. Neonatal anemia affected 26.6% of neonates in the exposed group and only 11.4% in the non-exposed group. IUGR was reported in 21.5% of exposed pregnancies versus 8.9% in the non-exposed group. Maternal anemia was significantly more frequent in the exposed group, affecting 48.1% of participants, compared to 17.7% in the non-exposed. Blood transfusions were required in 16.5% of the exposed group, whereas only 3.8% of the non-exposed group required this intervention. Oligohydramnios was diagnosed in 19% of the exposed group compared to 6.3% of the non-exposed group. The numerical trends consistently indicated higher rates of complications among women with beta-thalassemia minor and low hemoglobin levels across all measured outcomes. These results support the hypothesis that thalassemia minor with low hemoglobin levels is associated with increased risk of adverse maternal and neonatal outcomes.

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**Table 1: Demographic Characteristics of Study Participants (n = 158)**

| Variable | Exposed Group (n=79) | Non-Exposed Group (n=79) |
|---|---|---|
| Age (years) | 28.6 ± 4.5 | 29.2 ± 4.2 |
| Hemoglobin Level (g/dL) | 9.1 ± 0.7 | 11.3 ± 0.6 |
| BMI (kg/m²) | 24.8 ± 2.3 | 25.1 ± 2.0 |
| Socioeconomic Status | | |
| Lower | 38 | 27 |
| Middle | 30 | 34 |
| Upper | 11 | 18 |
| Occupation Status | | |
| Employed | 22 | 26 |
| Unemployed | 57 | 53 |
| Residence | | |
| Rural | 49 | 42 |
| Urban | 30 | 37 |
| Education | | |
| Primary | 23 | 18 |
| Middle | 31 | 33 |
| Higher | 25 | 28 |
| Consanguineous Marriage | | |
| Yes | 45 | 32 |
| No | 34 | 47 |

**Table 2: Adverse Feto-Maternal Outcomes in Exposed and Non-Exposed Groups**

| Adverse Outcome | Exposed Group (n=79) | Non-Exposed Group (n=79) |
|---|---|---|
| Preterm Birth | 19 | 8 |
| Low Birth Weight | 26 | 12 |
| Neonatal Anemia | 21 | 9 |
| Intrauterine Growth Restriction (IUGR) | 17 | 7 |
| Maternal Anemia | 38 | 14 |
| Blood Transfusions | 13 | 3 |
| Oligohydramnios | 15 | 5 |

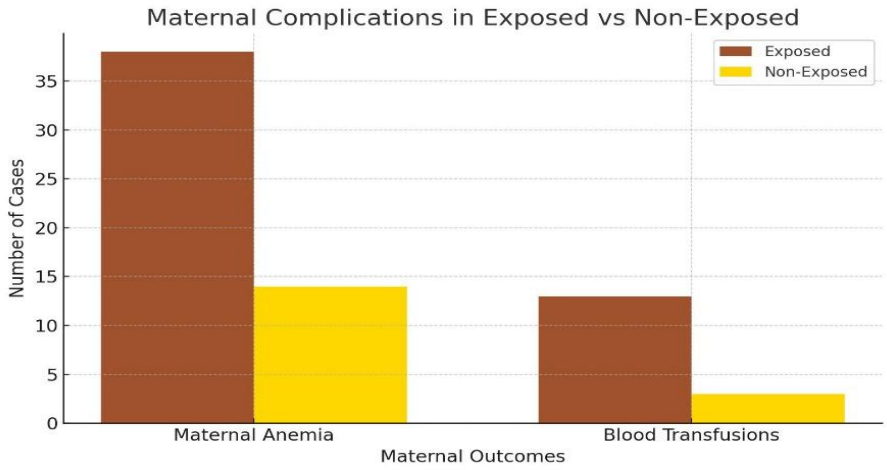


*Figure 2 Maternal Complications in Exposed vs non-exposed*

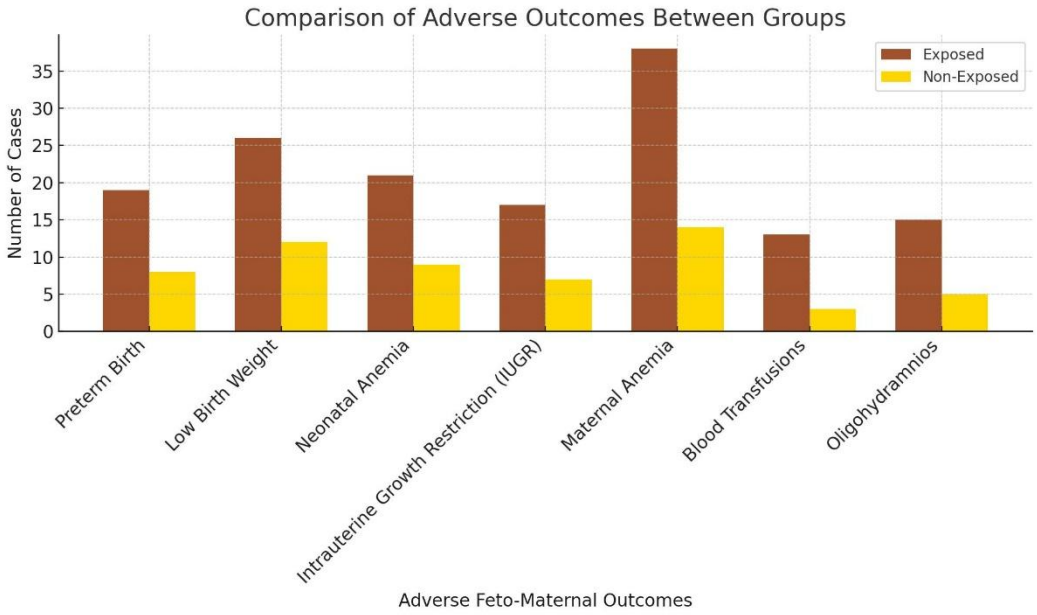


*Figure 2 Comparison of Adverse Outcomes Between Group*

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## DISCUSSION

The findings of this study demonstrated a clear association between beta-thalassemia minor and an increased risk of adverse maternal and neonatal outcomes during pregnancy. Women with beta-thalassemia minor and low hemoglobin levels were significantly more likely to experience preterm birth, low birth weight, neonatal anemia, intrauterine growth restriction (IUGR), maternal anemia, need for blood transfusions, and oligohydramnios compared to non-thalassemic women with normal hemoglobin levels. These results are aligned with recent literature that reinforces the clinical burden associated with thalassemia minor during pregnancy. Case-control studies showed that women with beta-thalassemia minor had significantly lower hemoglobin levels, gestational age, and neonatal birth weight compared to controls, alongside higher frequencies of preterm labor, caesarean delivery, and neonatal unit admissions (17,18). Similarly, a large cohort study found a significant increase in long-term hematological morbidities among offspring of thalassemic mothers, highlighting the enduring impact of prenatal anemia and iron dysregulation (19). Our results also confirmed maternal anemia as one of the most prevalent complications in the exposed group, observed in nearly half of the participants. This supports the findings of a study which reported consistently lower hemoglobin and hematocrit levels throughout pregnancy and postpartum among thalassemia carriers (20). Moreover, another study noted significant placental histological abnormalities in thalassemia minor pregnancies, which may explain the increased rates of IUGR and low birth weight observed in our study (21). One strength of this study is its prospective cohort design, which allowed for close monitoring of outcomes over time and reduced the risk of recall bias. Additionally, the inclusion of well-matched exposed and non-exposed groups enhanced internal validity. Standardized diagnostic criteria and direct investigator-led follow-up further improved the reliability of recorded outcomes.

However, certain limitations must be acknowledged. The use of non-probability consecutive sampling may have introduced selection bias, limiting the generalizability of the findings to wider populations. Furthermore, the sample size was calculated based solely on caesarean section rates rather than encompassing all outcome measures, which may limit statistical power for some secondary outcomes. Another limitation was the lack of data on iron supplementation practices, chelation therapy, or other interventions during pregnancy, which may have influenced both maternal and neonatal outcomes. Despite these limitations, the study provides essential insight into the overlooked clinical implications of beta-thalassemia minor during pregnancy, particularly in resource-constrained settings where antenatal screening may not be uniformly available. The results reinforce the need for early identification of at-risk women and the incorporation of multidisciplinary care involving hematology and maternal-fetal medicine specialists. Future studies should aim to include larger multicenter populations and utilize probability-based sampling strategies to enhance external validity. In-depth exploration of iron metabolism, placental perfusion, and fetal oxygenation using advanced imaging and biochemical markers may also offer mechanistic understanding (22). Moreover, randomized trials evaluating the benefits and risks of proactive transfusion strategies or iron modulation therapies could guide evidence-based interventions in this population. In conclusion, this study adds to the growing body of evidence that beta-thalassemia minor, particularly when accompanied by low hemoglobin levels, is not as benign in pregnancy as traditionally perceived. The condition is associated with multiple adverse feto-maternal outcomes, emphasizing the importance of vigilant antenatal surveillance, individualized care plans, and policy-driven screening initiatives.

## CONCLUSION

This study concluded that beta-thalassemia minor with low hemoglobin levels is significantly associated with increased risks of adverse feto-maternal outcomes, including preterm birth, low birth weight, neonatal anemia, and maternal complications. These findings emphasize the importance of routine antenatal screening, close hematological monitoring, and multidisciplinary care in pregnancies affected by thalassemia minor to improve maternal and neonatal prognosis, particularly in resource-limited settings.

## AUTHOR CONTRIBUTION

| Author | Contribution |
|---|---|
| Aysha Rahman* | Substantial Contribution to study design, analysis, acquisition of Data<br>Manuscript Writing<br>Has given Final Approval of the version to be published |
| Tayaba Mazhar | Substantial Contribution to study design, acquisition and interpretation of Data<br>Critical Review and Manuscript Writing<br>Has given Final Approval of the version to be published |
| Qurat Ul Ain Zaman | Substantial Contribution to acquisition and interpretation of Data<br>Has given Final Approval of the version to be published |
| Aleena Javed | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Nayab Rawail | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Zeenat Afridi | Substantial Contribution to study design and Data Analysis<br>Has given Final Approval of the version to be published |

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