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Exploring the Spectrum: Hemoglobinopathies in Pregnancy and their Clinical Implications

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Abstract

The present study aimed to investigate the maternal and fetal outcomes of pregnant women presenting to a tertiary healthcare facility with beta thalassemia trait, hemoglobinopathy E, and sickle cell trait. This retrospective study of a series of cases presented to a tertiary healthcare facility, Saveetha Medical College, Thandalam, Chennai between June 2023 and December 2023. The case series included nine pregnant women aged between 21 - 31 years with varying obstetric histories. Most were multigravida with 60.0% having previous caesarean sections. Gestational age at diagnosis ranged from 17 - 35 weeks with one case diagnosed preconception. Mean hemoglobin levels before correction were 8.5 gm/dL, rising to 10.3 gm/dL post-correction. Hematological parameters varied within normal ranges. HPLC revealed heterozygous hemoglobinopathy E, beta thalassemia trait or sickle cell trait in equal proportions. Most deliveries occurred at term, with varying modes of delivery including emergency caesarean sections and vaginal deliveries. Incidence of postpartum hemorrhage and preterm premature rupture of membranes was infrequent, though one case of each occurred. No instances of pre-eclampsia, foetal growth restriction, or maternal or foetal deaths were reported. Neonatal outcomes were generally favorable, with all babies born alive, mostly at term, and satisfactory APGAR scores. Two cases were born with low birth weight. Early and accurate diagnosis facilitated tailored interventions, ultimately lead to positive maternal and neonatal outcomes. These cases serve as poignant reminders of the importance of comprehensive antenatal care, genetic counselling, and specialised management strategies for individuals affected by hemoglobinopathies.

Keywords: *Beta Thalassemia Trait, Foetal Outcomes, Hemoglobinopathies, Hemoglobinopathy E, Lower Segment Cesarean Section (LSCS), Maternal Outcomes, Sickle Cell Trait.*

Introduction

Hemoglobinopathies encompass a diverse array of hereditary disorders affecting the synthesis and functionality of hemoglobin. They represent the most prevalent single-gene diseases globally, varying their prevalence across different regions due to genetic and historical migration influences [1]. According to the World Health Organization (WHO), approximately 5.0% of the global population are carriers of the inherited hemoglobinopathies. Annually, an estimated 9 million carriers of worldwide become pregnant,

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resulting in around 332,000 affected the conceptions or births, particularly notable in nations with lower to moderate incomes [2]. Traditionally concentrated in tropical regions, hemoglobinopathies have dispersed globally due to population movements [3]. In India, the incidence of sickle cell disease varies between 1 - 44%, while the occurrence of the thalassemia trait ranges from 3 - 17%, respectively [4]. Specific communities in India face heightened prevalence due to factors such as consanguinity, caste, and regional endogamy, posing significant public health challenges [4, 5]. Hemoglobinopathies encompass a spectrum of conditions, ranging from benign to severe ailments necessitating regular blood transfusions and intensive medical management [6]. Beta thalassemia affects 1.5% of the global population, while hemoglobin disorders afflict 7.0%. Worldwide, approximately 7,000 new-borns are diagnosed with beta thalassemia major annually. In India, sickle cell disease (Hb S), haemoglobin E (Hb E), and haemoglobin D (Hb D) are the most prevalent abnormal haemoglobin types, exhibiting regional disparities [7]. Advancements in hematological care have led to increased longevity and improved quality of life for women with hemoglobinopathies, resulting in higher rates of pregnancies in this demographic [8]. However, pregnancy-induced physiological changes can exacerbate underlying hemoglobin abnormalities, potentially leading to complications during childbirth [9]. While pregnancy typically induces mild dilutional anaemia due to increased blood volume, women with haemoglobin disorders may experience substantial drops in haemoglobin levels, posing risks of hypoxia and adverse outcomes for both mother and foetus [10-13]. Severe maternal anaemia can lead to complications such as premature births, spontaneous abortions, low birth weight, and foetal deaths. High-Performance Liquid Chromatography (HPLC) surpasses standard haemoglobin electrophoresis as a superior method for accurately identifying and quantifying aberrant haemoglobin variants and thalassemia traits [14]. HPLC stands as the crucial and credible technique for the early detection and management of various genetic disorders, particularly prevalent in the Indian subcontinent, where beta thalassemia trait incidence is notably elevated [15]. Against this background, the objective of the present study was to investigate the maternal and fetal outcomes of pregnant women with beta thalassemia trait, hemoglobinopathy E, and sickle cell trait, presenting to a tertiary healthcare facility.

Materials and Methods

This was a retrospective study involving a series of 9 cases that were presented to a tertiary healthcare facility, Saveetha Medical College, Thandalam, Chennai, between June 2023 and December 2023. The study included pregnant women presenting with confirmed diagnosis of beta thalassemia trait, hemoglobinopathy E, and sickle cell trait; singleton pregnancy; received antenatal care and delivered at Saveetha Medical College with medical records that included complete data on maternal and foetal outcomes. However, pregnant women with other significant comorbidities that could independently impact the maternal or foetal outcomes; multiple gestations; and incomplete medical records were excluded. The study was approved by the Institute Human Ethics Committee (IHEC). From the medical records, we obtained sociodemographic information, gestational age at booking/pregnancy registration, prenatal care details, obstetric complications (including pre-eclampsia, gestational diabetes, gestational hypertension), mode of delivery, birth outcomes (including birth weight, gestational age at delivery), neonatal complications (including neonatal intensive care unit (NICU) admission, respiratory distress syndrome), and maternal complications (including maternal mortality,

vaso-occlusive crises). The present study included 9 cases confirmed with high-performance liquid chromatography (HPLC). The data was anonymized during analysis and reporting.

Results – Case Series

This case series included a total of nine cases. The pregnant women were between 21 and 31 years old, with a mean (SD) of 26.4 years (3.6). The obstetric scores varied, with a mix of primigravida and multigravida cases. Four of the nine cases were primigravida (44.4%); three of the five (60.0%) multigravida (55.6%) had previous cesarean section; and the remaining two (40.0%) had a previous normal vaginal delivery. The gestational age at diagnosis ranged from 17 to 35 weeks; one case was diagnosed preconception (11.1%). The mean (SD) hemoglobin levels among pregnant women included in the present study was 8.5 gm/dL (0.8) (varied from 6.9 to 9.8 g/dL before correction). The standard anemia correction methods included packed red blood cell (PRBC) transfusions (ranging between one to two units) and iron sucrose doses (ranging between two to eight doses). After the correction, the mean (SD) hemoglobin levels were 10.3 gm/dL (0.7). The mean (SD) levels of packed cell volume (PCV), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV, ranged from 58.4 to 75.9 fl), mean corpuscular hemoglobin concentration (MCHC), platelets (ranged from 1.53 to 3.77 lakh/mm^3), and RBC counts were 27.9 (2.0), 20.5 (2.0), 66.8 (5.9), 30.6 (1.5), 2.8 (0.8), and 4.2 (0.4), respectively. The results of HPLC showed that patients presented with heterozygous hemoglobinopathy E (33.3%), beta thalassemia trait (33.3%), or sickle cell trait (33.3%). The paternal testing revealed average results (100%). Of the seven cases for whom information on gestational age at delivery was available, the gestational age was between 35 weeks five days to 40 weeks one day. The mode of delivery varied, including emergency lower segment cesarean section (LSCS) (4/8 cases, 50.0%; indication was breech in one case and fetal distress in another; indication unknown in two cases) and standard vaginal delivery with or without rupture of membranes (along with right mediolateral episiotomy) (Table 2).

The results showed that the incidence of postpartum hemorrhage (PPH) and preterm premature rupture of membranes (PROM) was infrequent. One patient with beta thalassemia trait presented with mild PPH and was managed with Inj. Methergine 0.2mg IM and Inj. Carboprost 0.25mg. The incidence of PROM was 33.3% – one at 38 weeks three days, another at 37 weeks three days, and the third case at 35 weeks five days. Preterm labor occurred in one case (36 weeks two days); the patient had a case of beta thalassemia trait. There were no instances of pre-eclampsia, fetal growth restriction (FGR), antepartum hemorrhage (APH), or sepsis. One patient with sickle cell trait had gestational diabetes mellitus (GDM), for which the patient was on Inj. Insulin. Though none of the pregnant women had oligohydramnios, two cases had an amniotic fluid index close to the lower bound at 6 and 7 centimeters (Table 2). The neonatal outcomes were generally favorable, with all babies born alive, mostly at term (6/7 cases, 85.7%), and satisfactory APGAR scores. The APGAR score is a test performed on the neonates to check their appearance, pulse, grimace, activity, and respiration (Table 1). The mean (SD) birth weight was 2.7 kilograms (0.5) – two cases were born with low birth weight (28.6%). No maternal or fetal deaths were reported in the cases included in the present study.

Table 1. APGAR Score Table

INDICATOR	0 POINTS	1 POINT	2 POINTS
A- Appearance	Blue, pale	Pink body; blue Extremities	Pink
P – Pulse	Absent	Below 100 bpm	Over 100 bpm
G – Grimace	Floppy	Minimal Response to stimulation	Prompt response to stimulation
A -Activity	Absent	Flexed arms and legs	Active
R - Respiration	Absent	Slow and irregular	Vigorous cry
Severely depressed 0-3, Moderately depressed 4-6, Excellent condition 7-10			

Table 2. Characteristics of Cases Included in the Present Study

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**	**Patient 9**
Age (in years)	23	27	30	30	24	21	28	24	31
Obstetrics score	Primi	G2P1L1	Primi Previous LSCS	G2P1L1 Previous LSCS	Primi	G2P1L1 Previous LSCS	G3P2L1D1 Previous NVD (normal vaginal delivery)	Primi	G3P1L1A1 Previous NVD
Gestational age at diagnosis	17 weeks	31 weeks	35 weeks	34 weeks	28 weeks	32 weeks	26 weeks	Preconception	26 weeks

HPLC	Hemoglobinopathy E, heterozygous	Hemoglobinopathy E, heterozygous	Hemoglobinopathy E, heterozygous	Beta thalassemia trait	Beta thalassemia trait	Beta thalassemia trait	Sickle cell trait	Sickle cell trait	Sickle cell trait
Anaemia correction	1-unit PRBC	2-unit PRBC	Eight doses iron sucrose at 20 weeks	Seven dose iron sucrose at 26 weeks	2-unit PRBC	1-unit PRBC	2-unit PRBC	1 PRBC and 2 dose iron sucrose	1-unit PRBC AND 5 dose iron sucrose
Haemoglobin	8.8	6.9	9.8	8.7	8.4	9	8.2	8.1	8.6
Hb after correction	10.9	11.2	10.9	9.3	9.8	9.6	10.9	9.8	10.5
PCV	27	24.3	32	28.7	28.9	28.5	27.5	27.2	27.7
MCH	20	16.6	21.3	20.6	21.1	21.6	21.2	18.1	23.6
MCV	61.2	58.4	65.4	67.8	72.4	68.3	71.1	60.7	75.9
MCHC	32.6	28.4	32.5	30.3	29.1	31.6	29.8	29.8	31
Platelets	2.86	3.77	3.54	3.62	2.96	3.31	1.68	2.20	1.53
RBC Count	4.41	4.16	4.89	4.23	3.99	4.17	3.87	4.48	3.65
Paternal testing	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
GA at delivery	38 weeks, 3 days	40 weeks one day	38 weeks four day	36 weeks, 2 days	39 weeks, 5 days		37 weeks three days	35 weeks five days	
Mode of delivery	Emergency LSCS (breech)	LN with RMLE	LN WITH RMLE	Emergency LSCS with sterilisation	Emergency LSCS for foetal distress	Emergency LSCS	LN with RMLE	LN WITH RMLE	
PPH	No	No	No	mild PPH - medically managed	No		No	No	

PROM	At 38 weeks, 3 days	No	No	No	No	No	37 weeks, 3 days	35 weeks five days	No
Preterm	No	No	No	36 weeks 2 days	No	No	No	Yes	No
Pre-eclampsia	No	No	No	No	No	No	No	No	No
GDM or Diabetes or GHTN	No	No	No	No	No	No	No	No	GDM on insulin
FGR	No	No	No	No	No	No	No	No	No
APH	No	No	No	No	No	No	No	No	No
Sepsis	No	No	No	No	No	No	No	No	No
Oligohydramnios	No	No	No	AFI: 6cm	No	AFI: 7cm	No	No	No
Alive/stillbirth	Alive	Alive	Alive	Alive	Alive		Alive	Alive	
Term/preterm	Term	Term	Term	Term	Term		Term	Preterm	
Birth weight (in kgs)	3.14	2.81	3.14	2.92	3.00		1.97, SGA	1.88	
APGAR SCORE	8/10, 9/10	8/10, 9/10	8/10, 9/10	8/10, 9/10	8/10, 9/10		8/10, 9/10	8/10, 9/10	

Discussion

The present study aimed to investigate the maternal and fetal outcomes of pregnant women presenting to a tertiary healthcare facility with beta thalassemia trait, hemoglobinopathy E, and sickle cell trait. The current study involved nine cases of hemoglobinopathy: The age of pregnant women in the study ranges from 21 to 31 years, reflecting a relatively young cohort. This demographic distribution is consistent with the childbearing age range and underscores the importance of understanding the implications of hemoglobinopathies on maternal and fetal health in this population [16, 17]. The study population comprised a mix of primigravida and multigravida cases, with a slightly higher proportion of multigravida cases (55.6%). Notably, a majority of the multigravida cases had a history of previous cesarean section, highlighting the potential obstetric complexities associated with repeat cesarean deliveries in women with hemoglobinopathies [18]. The wide range of gestational ages at diagnosis (17 to 35 weeks) underscores the variability in the timing of diagnosis of hemoglobinopathies during pregnancy. Early diagnosis, ideally preconception, allows for the timely initiation of prenatal care and interventions to optimize maternal and fetal outcomes [19].

The mean hemoglobin level among pregnant women included in the study was 8.5 g/dL before correction, indicating moderate to severe anemia. Standard methods of anemia correction included packed red blood cell (PRBC) transfusions and iron sucrose doses, resulting in a mean hemoglobin level of 10.3 gm/dL after correction. These results emphasize the critical need for careful monitoring and effective management of anemia in pregnant women with hemoglobinopathies to prevent adverse maternal and fetal outcomes [20]. The study provides insight into various hematological parameters, including packed cell volume, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, and red blood cell count. These parameters indicate hematological status and can guide clinical management and monitoring in pregnant women with hemoglobinopathies [21].

This study reflects the diverse genetic background of the population and emphasizes the need to account for multiple hemoglobinopathies in prenatal care. The average results of paternity testing of HPLC suggest that the hemoglobinopathies observed in pregnant women were inherited in an autosomal recessive manner [22]. This finding highlights the significance of genetic counseling and screening for both partners to assess the risk of hemoglobinopathies in offspring [23]. The range of gestational ages at delivery (35 weeks five days to 40 weeks one day) indicates variability in the timing of deliveries among women with hemoglobinopathies. This variability may be influenced by factors such as maternal health status, fetal well-being, and obstetric complications, emphasizing the need for individualized prenatal care and delivery planning. The diverse modes of delivery observed in the study, including emergency LSCS and expected vaginal delivery, underscore the importance of obstetric management tailored to the specific needs of each patient. The indications for emergency LSCS, such as breech presentation and fetal distress, highlight the potential obstetric complications associated with hemoglobinopathies during labor and delivery [24] (Table 2). Close monitoring of maternal and fetal well-being, timely intervention for obstetric complications, and clear communication between healthcare providers and patients are essential to optimize maternal and neonatal outcomes.

The low incidence of PPH and PROM observed in the study population is noteworthy. Despite the rarity of these complications, it is essential to recognize and manage them

promptly when they occur. The case of mild PPH, which was managed medically in a patient with beta thalassemia trait, highlights the importance of appropriate pharmacological management to prevent adverse outcomes. This finding corroborates with that reported by Hanprasertpong et al., which states that the thalassemia trait condition does not affect the risk of gestational diabetes, postpartum hemorrhage, stillbirth, preterm birth, and puerperal morbidity. However, the study did suggest that pre-eclampsia should be warranted (closely monitored), especially among nulliparous (first-time mothers) and high-BMI pregnant women [25]. While the overall incidence of preterm birth was low, it is notable that one case of preterm birth occurred in a patient with beta thalassemia trait. The absence of pre-eclampsia, fetal growth restriction, antepartum hemorrhage, or sepsis in the study population is reassuring. However, it is essential to recognize that the sample size may affect the generalizability of these results, and additional research is warranted to confirm the absence of these complications in larger cohorts. Identifying GDM in one patient with sickle cell trait highlights the importance of screening for and managing comorbid conditions during pregnancy [26]. Timely intervention with insulin therapy can help reduce the risks associated with GDM and optimize maternal and fetal outcomes. Close monitoring and prompt intervention are essential to ensure maternal and neonatal well-being. Although none of the pregnant women had oligohydramnios, the presence of two cases with an amniotic fluid index close to the lower bound raises awareness of the need for ongoing surveillance of amniotic fluid levels in women with hemoglobinopathies to detect and manage potential complications such as fetal distress [27-29]. Overall, neonatal outcomes were generally favorable, with all babies born alive and mostly at term. However, the low birth weight in two cases, in which the term low birth weight was small for gestation, highlights the importance of monitoring fetal growth and implementing appropriate interventions to optimize birth weight and neonatal health.

Conclusion

In conclusion, this case series highlights the diverse range of hemoglobinopathies (beta thalassemia trait, hemoglobinopathy E, and sickle cell trait) encountered in pregnancy and underscores the pivotal role of HPLC in antenatal screening. Early and accurate diagnosis facilitated tailored interventions, ultimately leading to positive maternal and neonatal outcomes. These cases are poignant reminders of the importance of comprehensive antenatal care, genetic counseling, and specialized management strategies for individuals affected by hemoglobinopathies. By employing a multidisciplinary approach and leveraging advanced diagnostic techniques like HPLC, healthcare providers can optimize care for this unique patient population, ensuring the best possible outcomes for both mother and child.

Conflict of Interest

Authors declare no conflict of interest to this work.

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