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Congenital hemolytic anaemias in pregnancy – experience in a tertiary care hospital in South India

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Abstract
Objective: To study the maternal and foetal outcomes in pregnancies complicated by congenital hemolytic anaemias.
Material and Methods: A retrospective descriptive study was carried out on pregnant women with hemolytic anaemias who delivered at SJMCH between January 2011 and January 2016. Antenatal and labour records were reviewed. Demographic variables like maternal age, parity, booking status, consanguinity, cause of haemolytic anaemia and time of diagnosis were noted. The primary outcome measures studied were - severity of anaemia, obstetric and medical complications, transfusion of blood and blood products and mode of delivery. Neonatal outcomes, need for ICU admission and duration of hospital stay were the secondary outcome measures studied. Data are presented as descriptive statistics, including means and percentage.
Results: Prevalence of congenital hemolytic anaemias was 0.3% (38/12420). 20 had Beta-Thalassemia; 9 Sickle cell anaemia, 7 Hereditary Spherocytosis, and 2 had enzyme defects. 13% had mild, 55% moderate, 23% severe and 5% very severe anaemia. The obstetric complications noted were pre-eclampsia (7.8%), abortions and preterm labour in 10% each, oligohydramnios and puerperal sepsis in 13% each, IUGR (23%), infections (29%), and foetal distress (31.5%). 47% had vaginal deliveries, and 52% caesarean deliveries. 42% required antenatal, 13% intrapartum and 36% postpartum transfusion of blood products. The mean birth weight of babies was 2.65 kg. 5% had PPH, none required ICU care.
Conclusion: Successful pregnancy outcomes can be achieved with prompt diagnosis, patient education, screening, genetic counselling and prenatal diagnostic testing of foetus and management in a tertiary care hospital by a multidisciplinary approach.

Keywords: Pregnancy outcomes, congenital hemolytic anemias, beta thalassemia, sickle cell anemia, hereditary spherocytosis

Introduction
Hemolytic anaemias are conditions where red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over. These anaemias tend to be more severe during pregnancy as pregnancy is an immune-suppressed state. Inherited forms of hemolytic anaemia are lifelong conditions that may require ongoing treatment. Acquired forms of hemolytic anaemia may remit if the underlying cause is found and treated.
Pregnancy in congenital hemolytic anaemia's (CHA) is at increased risk of abortion, preterm labour, pre-eclampsia, infections, Caesarean delivery, medical intensive care unit (MICU) admission, maternal death, intrauterine growth restriction (IUGR), low birth weight (LBW), intrauterine death (IUD) and neonatal intensive care unit (NICU) admission [1-5]. Since most congenital hemolytic anaemias are autosomal recessive conditions, screening, counselling and prenatal diagnosis are essential components of prenatal care for these women [6]. The role of prenatal diagnostics tests and intensive foetal monitoring in utero warrant better antenatal care. Congenital hemolytic anaemias are showing a rising trend either due to improved diagnostic and therapeutic modalities or increased awareness in public. However, there is scant Indian literature regarding these anaemias. This study was hence done to look into the obstetric and neonatal outcomes and formulate management strategies for pregnant women with CHA.

Materials and Methods
A retrospective descriptive study was carried out on pregnant women with hemolytic anaemias who delivered at SJMCH between January 2011 and January 2016.

Only women with CHA were included. Anaemias due to other causes (nutritional, blood loss, microangiopathic hemolytic anaemia, acquired hemolysis) were excluded. Antenatal and labour records were reviewed. Demographic variables like maternal age, parity, booking status, consanguinity, cause of haemolytic anaemia and time of diagnosis were noted. The primary outcome measures studied were - the severity of anaemia at booking defined as per Indian Council for Medical Research criteria (mild as Hb of 10.9 – 10 g/dl; moderate as Hb of 7-9.9g/dl; severe as Hb of 4-6.9g/dl; very severe as Hb < 4g/dl) [7], the obstetric and the medical complications, transfusion of blood and blood products and the mode of delivery. The secondary outcome measures studied were – neonatal outcomes, need for ICU admission and duration of hospital stay. Data are presented as descriptive statistics, including means and percentage. The Institutional Ethics Committee approved the study.

Results

A total of 12420 women delivered at SJMCH during the study period, of whom 56 were detected to have hemolytic anaemias accounting for the prevalence of 0.45%. 38 of the 56 women had CHA (0.3%). Of these 38 women, 20 had Beta-Thalassemia; 9 had Sickle cell anaemia, 7 had Hereditary Spherocytosis and 2 had enzyme defects (1 had pyruvate kinase deficiency, and 1 had congenital nonspherocytic hemolytic anaemia).

The demographic characteristics have been shown in table1; severity of anaemia in table 2; obstetrics and medical complications in table 3; intrapartum details in table 4; neonatal outcome in table 5.

The mean maternal age was 25.35 years in CHA. 44% and 55% were primi multigravidae respectively. 82% of the case was booked. There was a history of consanguinity in 31.5% of mothers. 52% had a prior diagnosis of CHA; 2.6% did not have anaemia, 13% had mild, 55% had moderate, 23% had severe anaemia and 5% very severe anaemia. The obstetric complications noted were pre-eclampsia (7.8%), abortions, preterm labour and previous caesarean delivery in 10% each, oligohydramnios, precipitate labour and puerperal sepsis in 13% each, IUGR (23%), infections (29%), bad obstetrics history (BOH) (21%) and foetal distress (31.5%). 15% had jaundice. 47% had vaginal deliveries, and 52% had caesarean deliveries. 42% required antenatal, 13% intrapartum and 36% postpartum transfusion of blood products. The mean gestational age at delivery was 38.5 weeks, mean duration of labour was 2.7 hours; mean blood loss was 343 ml; 5% had PPH, none required ICU care, mean birth weight of babies was 2.65 kg, the average duration of hospital stay was 8 days.

Beta Thalassemia constituted 52.6% pregnant women with CHA with a prevalence of 0.16%. Of the 20 women, 18 had Beta Thalassemia trait, 1 had Beta Thalassemia intermedia, and 1 had HbH disease. Only 1 case had infertility, and all had conceived within 2.5 years of married life. Only 3 women (15%) had undergone a prenatal diagnostic technique (2 amniocenteses, 1 Chorionic villus sampling) during the current pregnancy, of which only one foetus was detected to have beta Thalassemia minor. 65% had moderate anaemia and 15% severe anaemia. 25% had BOH, 20% had IUGR, antenatal infections, previous Caesarean delivery and foetal distress each. 30% had puerperal sepsis and 10% had postpartum haemorrhage (PPH). 45% had vaginal deliveries, 55% had caesarean deliveries for obstetrics indications. 30% of women received a transfusion of blood products antenatally, 10% intrapartum and 35% of women received transfusions postnatally. 35% of babies required NICU admission for birth asphyxia, LBW, respiratory distress, prematurity or congenital heart disease.

The Beta-Thalassemia intermedia and the HbH disease women had a history of consanguinity; had received multiple transfusions in previous pregnancies; presented with severe anaemia, IUGR, foetal distress- meconium stained liquor; had Caesarean deliveries; received multiple transfusions antenatally or postnatally and had pyrexia postpartum.

Sickle cell disease was found in 9 pregnant women contributing to 23.6% of CHA, accounting for the prevalence of 0.07%. Sickle cell anaemia was seen in 3, Sickle beta-thalassemia in 4 and HbSC/ HbD and HbSC/Persistent foetal Haemoglobin in one each. Clinically significant Sickle cell crisis occurred in 2 out of 3 patients with Sickle cell anaemia, 3 out of 4 patients with Sickle beta-thalassemia and both patients with HbSC/HbD and HbSC/Foetal Hb. 55% had moderate anaemia and 33% severe anaemia. 55% had infections which included urinary tract infections, discharge per vagina, upper respiratory tract infection, chickenpox, typhoid and pyelonephritis. 44% each had abortion and IUGR, 33% had oligohydramnios, BOH, jaundice, precipitate labour and foetal distress. 11%had pre-eclampsia, preterm labour and hypothyroidism. Only 3 women needed induction of labour, and the remaining 6 went into labour spontaneously. 66% had vaginal deliveries, and 33% underwent a Caesarean section for foetal distress.77% had antenatal transfusions of blood products, 33% had intrapartum transfusions, and 66% had postnatal transfusions. There were no PPH or MICU admissions. 55.5% babies had NICU admissions for hypoglycaemia, jaundice or low birth weight.

Pregnant women with hereditary spherocytosis constituted 18.4% of CHA accounting for the prevalence of 0.05%. Hypertension, thrombocytopenia, hypothyroidism, reactive arthritis, preterm labour, preterm prelabour rupture of membranes, IUGR, post datism, jaundice and decreased foetal movements were noted in 14% each. 28% needed transfusions antenatally and 14% postnatally. 5 (71.47%) underwent Caesarean delivery for foetal distress (4 had meconium-stained liquor, 1 had variable decelerations); 28.5% women had vaginal deliveries. 71% had puerperal fever or sepsis. There were no MICU admissions. 42% babies had NICU admission for jaundice. None of them had low Apgar scores.

Both women with enzyme defects were primigravida who had a prior diagnosis of enzyme defects and antenatal infections; 1 had jaundice; 1 received an antenatal transfusion of blood products; 1 had foetal distress; 1 had a vaginal delivery, and 1 had a Caesarean delivery.

Discussion

The prevalence of congenital hemolytic anaemias in our study was 0.3%. The actual prevalence may be much more as many cases fail to reach the tertiary care centres for evaluation and management.

Haemoglobinopathies are the most frequent hereditary disorders in India [8], and this was true in our study, too. Beta Thalassemia is the most typical type of haemoglobinopathy seen in India [9]. With the availability of cheaper and simpler screening and diagnostic modalities like NESTROFT [10] and better transfusion services, more women are reaching the reproductive age group and conceiving. In our study, the mean maternal age was 25 years, and only one woman required evaluation for infertility, similar to study by Sheiner *et al* [11]. The successful pregnancies has encouraged women to attempt more pregnancies leading to an increase in the number of multigravidae, as was seen in our cohort too.

The type of haemoglobinopathies determines the outcome of pregnancy. Women with Beta-Thalassemia minor or trait have better outcomes with less adverse events in pregnancy [4, 5]. In contrast, those with Beta-Thalassemia intermedia/HbE/HbS variants are more transfusion dependent with serious maternal and foetal complications [12-14].

Preconceptional counselling must be offered to such couples where the need for screening the partner and prenatal diagnostic tests must be emphasized, especially in our Indian society where consanguineous marriages are common [6]. In our study, only 15% had undergone a prenatal diagnostic test.

Majority of cases in our study was Beta-Thalassemia trait. The prognosis was good in those cases, corroborating reports by Sheiner *et al*. and Amoee *et al*. [6, 11]. Though there was a higher rate of moderate anaemia, infections, previous Caesarean deliveries and BOH, this was not significant. However, there is a trend towards an increase in IUGR, transfusions and Caesarean delivery. Chronic maternal anaemia leads to foetal hypoxia, IUGR, oligohydramnios increasing the risk of foetal distress and Caesarean delivery [5, 11, 15].

Women with Beta-Thalassemia intermedia and HbH disease usually present with severe anaemia, IUGR, foetal distress and meconium-stained liquor necessitating Caesarean deliveries. They require multiple transfusions (antenatally and intrapartum). Transfusions are a risk because of the development of alloantibodies [13, 14]. Fever is a common postoperative complication. Such women should deliver in a tertiary care set up with good blood banking and ICU services involving a multidisciplinary team of obstetrician, neonatologist and haematologist.

The prevalence of sickle cell disease in our study is low (0.07%). Sickle cell disease has more complications in pregnancy when compared to those with traits [16, 17]. In our study, sickle cell crisis was seen in 77% of patients. Higher incidence of pre-eclampsia, oligohydramnios, IUGR, preterm labour, infections were noted in our study compared to other authors [3, 17, 18]. Vaginal deliveries with precipitate labour were common in the trait and Beta Thalassemia variants. In contrast, Caesarean deliveries may be necessitated in the HbSS group due to foetal distress or meconium-stained liquor [17, 19]. Blood transfusions are usually required more so during the crisis. Optimizing Hb to 10 gm/dl before delivery, avoidance of hypoxia and hypotension, prevention of thromboembolism and use of low-dose aspirin to prevent pre-eclampsia are crucial steps for a successful outcome [16]. In contrast to previous studies where IUGR and LBW are common [3, 18], our study reports a mean birth weight of 2.5kg. Also, there was no PPH, ICU admissions or maternal or perinatal mortality compared to other studies [16].

The prevalence of Hereditary spherocytosis in our study was higher at 0.05% when compared to North Europe and America, where the incidence varies from 1:2000 to 1:5000 [20]. Hereditary spherocytosis is usually asymptomatic and may get unmasked in pregnancy. 85.7% in our study had anaemia compared to 42% in a study by Pajor *et al* [21]. Antenatal transfusions are not required unless there is anaemia. Maternal complications are infrequent and perinatal outcomes excellent [22]. The results of our study are in concurrence with Brabec *et al* [23], with few non-serious antenatal complications. There is an increased risk of Caesarean delivery for foetal distress due to hypoxia secondary to hemolytic anaemia. This could account for the increased blood loss during labour, as seen in our cohort.

In our study, only 2 women had undergone splenectomy and 2 had undergone cholecystectomy before pregnancy. None required splenectomy during pregnancy. There was no difference in the outcomes among women who had undergone splenectomy compared to those who had not. Splenectomy is an independent risk factor for preterm delivery [24]. It is associated with complications like Caesarean delivery, pneumonia during pregnancy, complications of anaesthesia and sedation during labour [24]. Successful laparoscopic splenectomies during pregnancy have been reported by Khanna *et al* and Allran *et al*. [20, 25] The indication for splenectomy during pregnancy depends on the severity of symptoms. Though various authors have advised against splenectomy during pregnancy because of associated complications like serious sepsis, perioperative morbidity to the mother and the foetus, thrombocytosis and thrombosis, none of the reported cases had such problems. Laparoscopic splenectomy should be done in the second trimester if warranted [20, 24]. Pneumococcal, meningococcal and hepatitis B vaccination, antibiotic and antimalarial prophylaxis is essential after splenectomy.

Both women with enzyme defects had mild anaemia with fewer complications and good maternal and neonatal outcomes.

The retrospective nature and low power of the study and lack of neonatal follow up are the limitations of this study.

A high index of suspicion of congenital anaemia is required when there is no response to iron therapy. Multidisciplinary approach in a tertiary care hospital equipped with good blood bank, ICU, hematology, obstetrics and neonatology services are the key to successful outcomes. Patient education, genetic counselling and prenatal diagnostic testing of the foetus is a must. Anticipation and aggressive management of complications yield optimal results. National programmes to target the congenital hemolytic anaemias are the need of the hour [26]. Successful pregnancy with good obstetric and perinatal outcomes is possible in women with congenital hemolytic anaemias.

Table 1: Demographic features

Demographic variables	Beta Thalassemia n-20	Sickle cell anaemia n-9	Hereditary Spherocytosis n-7	Enzyme defects n-2	Congenital hemolytic anaemia n-38
Mean maternal age (years)	27.5	25.3	25.1	23.5	25.35
Parity primi multi	9(45%) 11(55%)	1(11.1%) 8(88.8%)	5(71.4%) 2(28.5%)	2(100%)	17(44.7%) 21(55.3%)
Consanguinuity	9(45%)	1(11.1)	1(14.2%)	1(50%)	12(31.5%)
Unbooked cases	3(15%)	3(33.3%)	1(14.2%)	0(0)	7(18.4%)
Diagnosis prior to pregnancy	11(55%)	3(33.3%)	4(57.1%)	2(100%")	20(52.6%)

Table 2: Severity of anaemia

Severity of anaemia	Beta Thalassemia n(%)	Sickle cell anaemia n(%)	Hereditary Spherocytosis n(%)	Enzyme defect n(%)	Congenital hemolytic anaemia n(%)
No anaemia	0 (0)	0(0)	1 (14.2)	0(0)	1(2.6)
Mild anaemia	1 (5)	0 (0)	0 (0)	2(100)	5(13.15)
Moderate anaemia	13 (65)	5 (55.5)	3 (42.8)	0(0)	21(55.2)
Severe anaemia	5 (15)	3 (33.3)	3 (42.8)	0(0)	9(23.6)
Very severe anaemia	1(5)	1 (11.1)	0 (0)	0(0)	2(5.2)

Table 3: Obstetrical and medical complications

Obstetrics / Medical Complication	Beta Thalassemia n(%)	Sickle cell anaemia n(%)	Hereditary spherocytosis n(%)	Enzyme defects n(%)	Congenital hemolytic anaemias n(%)
Preeclampsia	1(5)	1 (11.1)	1 (14.2)	0(0)	3(7.8)
IUGR	4(20)	4 (44.4)	1 (14.2)	0(0)	9(23.6)
Oligohydramnios	2(10)	3 (33.3)	0 (0)	0(0)	5(13.15)
Infections	4 (20)	5 (55.5)	0 (0)	2(100)	11(28.9)
Preterm labour	2(10)	1 (11.1)	1 (14.2)	0(0)	4(10.5)
PROM	1(5)	0 (0)	1 (14.2)	1(50)	3(7.8)
Bad obstetrics history	5(25)	3 (33.3)	0 (0)	0(0)	8(21)
Abortion	0(0)	4 (44.4)	0 (0)	0(0)	4(10.5)
IUD	0(0)	2 (22.2)	0 (0)	0(0)	2(5.2)
Hypothyroidism	3(15)	1 (11.1)	1 (14.2)	1(50)	6(15.7)
Jaundice	1(5)	3 (33.3)	1 (14.2)	1(50)	6(15.7)
Previous Caesarean delivery	4(20)	0 (0)	0 (0)	0(0)	4(10.5)
Precipitate labour	2(10)	3(33)	0(0)	0(0)	5(13.15)
Foetal distress	4(20)	3(33)	4(57.1)	1(50)	12(31.5)
PPH	2(10)	0(0)	0(0)	0(0)	2(5.2)
Puerperal sepsis/ pyrexia	6(30)	2(22)	5(71.4)	0(0)	13(34.2)

Table 4: Intrapartum details

Intrapartum details	Beta Thalassemia	Sickle cell anaemia	Hereditary spherocytosis	Enzyme defect	Congenital hemolytic anaemias
Average duration of labour in hours	3.25 H	4.21 H	1.91H	1.5 H	2.7 H
Average blood loss in ml	322.5	262.5	412.5	375	343.125
Mode of delivery Vaginal Caesarean delivery	9(45%) 11(55%)	6(66.6%) 3(33.3%)	2 (28.6%) 5(71.4%)	1(50%) 1(50%)	18(47.36%) 20(52.6%)
Transfusion of blood products Antenatal Intrapartum Postpartum	6(30%) 2(10%) 7(35%)	7(77%) 3(33.3%) 6(66.6%)	2(28.5%) 0(0%) 1(14.2%)	1(50%) 0(0%) 0(0%)	16(42.1%) 5(13.15%) 14(36.8%)
Average duration of hospital stay (days)	7	10	8	7	8

Table 5: Neonatal outcomes

Neonatal characteristics	Beta thalassemia	Sickle cell anaemia	Hereditary Spherocytosis	Enzyme defects	Congenital hemolytic anaemias
Mean gestational age at delivery (weeks)	38	38	39	39	38.5
Mean birth weight (kg)	2.67	2.5	2.8	2.65	2.65
Low Apgar score	4 (20%)	2 (22.2%)	0 (0%)	0(0%)	6(15.7%)
NICU admission	7(35)	5 (55.5%)	3 (42.8%)	1(50%)	16(42.1%)
Term	17(85)	8 (88.8%)	6 (85.7%)	2(100%)	33(86.84%)
Preterm	3(15)	1 (11.11%)	1 (14.2%)	0(0%)	5(13.15%)

Conclusion

Successful maternal and fetal outcome in pregnancies complicated with congenital hemolytic anaemias can be achieved with prompt diagnosis, patient education, screening, genetic counselling and prenatal diagnostic testing of foetus and management in a tertiary care hospital by a multidisciplinary approach.

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