Malaysian J Pathol 2018; 40(2) : 149 – 152

SHORT COMMUNICATION

Pregnancy outcomes in women with non-transfusion dependent thalassaemia (NTDT): A haematology centre experience

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Abstract

Introduction: Non-transfusion dependent thalassaemia (NTDT) is a term used for thalassaemia patients who do not require lifelong regular transfusions for survival. Pregnancy in these women, whether spontaneous or through assisted reproductive technology, represents a challenge for the physician. *Materials and Methods:* The maternal and foetal outcomes of patients with NTDT followed up in a tertiary haematology centre over 6 months period were studied. A total of 36 pregnancies in 26 pregnant women with NTDT were analysed. *Results:* Among these women, all of the pregnancies resulted in successful delivery of singleton live-born neonates. There were four clinically distinct forms of NTDT among these women which include Hb E/β-thalassemia (mild and moderate forms), HbH disease, HbH-Constant Spring, and homozygous δβ-thalassemia. No blood transfusion was needed in 15 of the 36 pregnancies (41.6%). The lowest mean Hb level in which no blood transfusion was given was 8.21 g/dL. The mean of packed-cell units received during pregnancy was 6.95 units per pregnancy. There was no worsening of serum ferritin observed during pregnancy with mean serum ferritin pre- and post-pregnancy of 409.35 ug/L and 418.18 ug/L respectively. The mean gestational age at delivery was 38.6 weeks with no preterm delivery reported. The mean foetal birth weight was 2729 grams. There was no intrauterine growth restriction (IUGR) or congenital malformation. There was a case of small for gestational age (SGA) and a case of oligohydramnios. *Conclusion:* This study showed that pregnancy was possible, safe and has a favourable outcome in patients with NTDT with multidisciplinary care.

Keywords: Non-transfusion dependent thalassaemia, pregnancy, maternal outcome, neonatal outcome

INTRODUCTION

Non-transfusion dependent thalassaemia (NTDT) is a term used for thalassaemia patients who do not require lifelong regular transfusions for survival. The most common forms of NTDT are β-thalassaemia intermedia, haemoglobin (Hb) E/β-thalassaemia, and α-thalassaemia intermedia (HbH disease).[1] In general, these patients have a milder clinical phenotype compared to those with thalassaemia major. They can present as a severe disease, diagnosed between 2 to 6 years of age or they can remain asymptomatic until adulthood.[2] They often suffer from mild degree of anaemia with Hb level between 7 to 10 g/dL.[2] Pregnancy in these women, whether spontaneous or through assisted reproductive technology, represents a challenge for the physician. Chronic anaemia associated with these conditions can affect the outcome of the pregnancy, for example an increase in spontaneous abortions, preterm labor, and intrauterine growth restriction (IUGR).[3] The objective of this study was to review the maternal and foetal outcomes of patients with NTDT in a tertiary haematology centre.

MATERIALS AND METHODS

This is a retrospective observational study. All pregnant patients with underlying NTDT attending the thalassaemia clinic in Ampang Hospital from July 2015 to Dec 2015 were identified from the hospital electronic database. The maternal data reviewed were maternal age, types of NTDT, parity, lowest Hb level, transfusion requirement, serum ferritin pre- and

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post-pregnancy, obstetric complications (e.g. abortion, abruptio placentae and preterm labor), mode of delivery, and post-partum complications (e.g. post-partum haemorrhage and thrombosis). The neonatal data reviewed were foetal growth by ultrasonography, birth weight and the presence of any congenital malformations.

Patients had regular antenatal visits and combined clinics with a multidisciplinary team. They were followed up until 6 weeks post-delivery. During clinics follow-up, maternal Hb levels were monitored every 4 weeks with assessment of anaemia symptoms. For all pregnancies, early dating scans were performed prior to 12th week followed by detailed scans at 20th week. Thereafter ultrasonographic evaluation of foetal growth was done every 4 weeks from 24th week of gestation. The need for transfusion throughout pregnancy was documented.

The study was registered under the National Medical Research Register (NMRR), Malaysia. It was approved by the Medical Research & Ethics Committee (MREC), a centralised independent ethics committee for public hospitals in the country.
Approval code: NMRR-17-2386-38171 (IIR)

RESULTS

A total of 36 pregnancies in 26 pregnant women with NTDT were analysed. All of them had spontaneously conceived. Among these women, all of the pregnancies resulted in successful delivery of singleton live-born neonates. The demographic and clinical characteristics of the patients are shown in Table 1. The maternal age of patients ranged from 21 to 39 years with a median maternal age of 30.5 years. Sixteen women (44.4%) were primigravida. There were four clinically distinct forms of NTDT among these women, which include Hb E/β-thalassemia (mild and moderate forms), HbH disease, HbH-Constant Spring, and homozygous δβ-thalassemia. No blood transfusion was needed in 15 out of the 36 pregnancies (41.6%). The lowest mean Hb level in which no blood transfusion was given was 8.21 g/dL. The mean of packed-cell units received during pregnancy was 6.95 units per pregnancy. Among the 21 pregnancies that required transfusions, the number of blood units transfused ranged from once during the entire pregnancy to once every 3 weeks. Majority of the women received transfusion based on symptoms of anaemia, decreased Hb levels and to allow normal foetal growth. There was no worsening of serum ferritin observed during pregnancy with mean serum ferritin pre- and post-pregnancy of 409.35 ug/L and 418.18 ug/L respectively. The mean gestational age at delivery was 38.6 weeks with no preterm delivery reported. The mean foetal birth weight was 2729 grams. Four women underwent Caesarean sections (11.1%). Two of them were emergency cases due to pre-

TABLE 1: Demographic and clinical characteristics of pregnant women with NTDT

Baseline characteristics	N (%)
1. Total number of pregnancies, n	36
2. Maternal age, years	
Median	30.50
Range (min, max)	18 (21, 39)
3. Gravida, n (%)	
Primid	16 (44.4)
≥ 2	20 (55.6)
4. Diagnosis, n (%)	
HbH disease	5 (13.9)
HbH-Constant Spring	6 (16.7)
Hb E/β-thalassemia	24 (66.7)
Homozygous Hb δβ-thalassemia	1 (2.8)
5. Transfusion requirement, n (%)	
Never	15 (41.6)
Occasionally (< 4 times)	14 (38.9)
Frequently (≥ 4 times)	7 (19.4)
6. Serum ferritin, ug/L	
Pre-pregnancy, median	409.35
Post-pregnancy, median	418.18

eclampsia and foetal distress, while the other two were elective cases due to multiple previous scars. Post-delivery, these women received low-molecular-weight-heparin prophylaxis while in hospital, until 7 days and 6 weeks post-discharge following vaginal delivery and caesarean section respectively. There was no report of thrombotic events during both antepartum and postpartum period. None of the women developed any symptoms related to cardiac failure during pregnancies.

There were no cases of intrauterine growth restriction (IUGR) or congenital malformation. However, one of them had baby with small for gestational age (SGA), defined as infants with a birth weight <10th percentile for gestational age[5], detected at 30th week despite 4 weekly transfusions since 12th week of gestation. The mother underwent induction of labor (IOL) at 37th week. The baby weighed was 1890 grams with no evidence of congenital malformation. One woman developed oligohydramnios in which she required an IOL at 38th week of gestation. She required no transfusion throughout her pregnancy and delivered a healthy baby weighing 2500 grams.

DISCUSSION

Several small studies and case series have demonstrated favourable maternal and foetal outcomes in patients with β-thalassaemia major when close follow-up and intensive treatments were instituted.[4-7] Little is known about pregnancy performance in patients with NTDT. These patients usually have a disease with severity between the mild manifestations of thalassaemia trait and the severe symptoms of thalassaemia major.[1] Transfusion therapy is not currently a routine treatment approach for patients with NTDT. Initiating regular blood transfusions in such patients remains a hard decision because of the heterogeneity of the disease. Patients who would benefit from such a measure include those with delayed growth, recurrent infections, and hypersplenism.[8] However, these patients might become transfusion-dependent in the future. The physiologic anaemia of pregnancy secondary to the increase in plasma volume is aggravated in patients with NTDT, hence most pregnant women with underlying NTDT may need blood transfusion during their pregnancies, either intermittently or on a regular basis. Also, the greater Hb demand for normal foetal growth and development might necessitate initiation of transfusion.

There has been practice in many centres to administer transfusion therapy during pregnancy to keep Hb above 8.0 g/dL to ensure optimal foetal growth. However, this approach has not been proven beneficial to both mother and foetus.[9] The fear of initiating more transfusions during pregnancy is the development of alloantibodies. This can lead to haemolysis and aggravate the anaemia causing more complications as well as difficulty finding compatible blood.[10] The risk of alloimmunisation is 1-1.6% after transfusion of one blood unit.[11] This risk can be minimised when patient is transfused with fully phenotyped matched blood.[12] Another concern with transfusion therapy is the risk of iron overload, especially in NTDT patients who have already accumulated considerable amounts of iron due to increased intestinal absorption, a consequence of ineffective erythropoiesis. Therefore, the benefits of frequent transfusion to the mother and infant should be weighed against its negative effects. The use of iron chelating agent in pregnancy can be a potential problem due to its teratogenicity effect. However, this is not a problem in our patients, as none of them were receiving iron chelating agent prior to conception, with the mean serum ferritin pre-pregnancy recorded as 409.35 ug/L.

Our study has shown that a high proportion of patients, 41.6% were transfusion free throughout their pregnancies with no adverse outcome observed. The lowest Hb levels recorded with no transfusion required ranged from 6.7 to 9.7 g/dL, with a mean of Hb level of 8.21 g/dL. The patient with lowest Hb level of 6.7 g/dL was asymptomatic at that level at 27th week of gestation and her Hb level tested a week later was 7.4 g/dL. She was monitored continuously with no transfusion given. She gave birth to a healthy baby weighing 2800 grams at 38th week of gestation. All mothers were supplemented with folic acid throughout their pregnancies. There was one incident of small for gestational age (SGA) detected at 30th week of gestation despite 4 weekly transfusions since 12th week of gestation. This patient's lowest Hb level documented was 5.20 g/dL and was maintained at a mean Hb level of 7.48 g/dL with regular transfusions.

Pregnancy itself increases the risk of thromboembolism due to its underlying hypercoagulable state. Pregnant women with NTDT are expected to have an even higher risk compared to the general pregnant population. The prevalence of thrombotic events in patients

with β-thalassemia intermedia can reach up to 20%, compared to less than 1% in patients with β-thalassemia major.[13-15] Abnormalities of platelets and pathological red blood cells are believed to be the key factors causing hypercoagulability and subsequent thrombotic events, especially in splenectomised and transfusion-independent patients, making this pathophysiology highly relevant to patients with NTDT.[16] However none of our patients in the study developed such complications, both during the antepartum and postpartum periods.

Overall, this observational study did not show an increased risk of ante-, intra-, or postpartum maternal complications. There is also no report of high incidence of foetal complications. On the other hand, one study by Anwar *et al*[17], that included only a total of 9 pregnancies of mothers with β-thalassemia intermedia reported a high incidence of IUGR, complicating 57.1% of cases and an incidence of unexplained intrauterine foetal death.

In conclusion, pregnancy in patients with NTDT is possible and can have a favourable outcome provided there is a multidisciplinary care among the obstetricians and haematologists, with close maternal and foetal surveillance.

ACKNOWLEGEMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this article and Law Kian Boon of Clinical Trial Unit, National Clinical Research Centre, MOH for his critical review of the paper.

Conflict of interest: There is no conflict of interest to declare.

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