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Prenatal Diagnosis Leads to Early Diagnosis of Transfusion-Dependent Thalassemia and Better Growth Outcomes

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Abstract

Thalassemia is the most common hematological transfusion-dependent disease in Thailand. Even though prenatal diagnosis (PND) can detect the condition, many new cases are diagnosed in pediatric practice. This study assessed the clinical outcome of patients with thalassemia who did PND. One hundred and six participants (53 female, 50%), with a median age of 8.5 years (Interquartile range [IQR] 8.00), were enrolled in the study. Twenty-one participants (19.8%) were prenatally diagnosed with thalassemia, with a median age of 8 years (IQR 9.00), 16 were diagnosed with transfusion-dependence thalassemia (TDT), and 5 participants were diagnosed with non-TDT. Another 80.2% did not prenatally diagnose, with a median age of 9 years (IQR 8.00). The PND group found early diagnosis compared with a non-PND group, at a median age of 6 months versus 15 months. There was a significant early diagnosis ($P < .001$). Furthermore, the participants' height for age z-score was significantly superior in the PND group ($P = .018$). Even though the result of PND was abnormal, the parents still willing to continue with the pregnancy. The reason was they wanted to have a child. However, their child may require lifelong transfusion therapy.

Keywords

prenatal diagnosis, transfusion-dependent, thalassemia, outcome

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Introduction

Thalassemia is one of the most common hematologic inherited disorders in the world. Approximately 300 000 children are diagnosed with thalassemia each year, representing a significant public health problem in many areas of the world.[1] In Thailand, about 25% of the population are thalassemia carriers.[2] Given the carriers' high prevalence, around 9000 patients per year are diagnosed with thalassemia.[3]

Thalassemia patients have a broad clinical spectrum ranging from asymptomatic, non-transfusion dependent thalassemia (NTDT), transfusion-dependence thalassemia (TDT), and fetus die in utero.[4] Chronic anemia in thalassemia results in growth retardation, skeletal deformities and extramedullary erythropoiesis.[5] The cost estimation to manage a single case of blood transfusions combined with iron chelating therapy (BT-ICT) in Thailand, based on desferrioxamine (DFO) as an iron chelator, is 6 million Thai Baht (THB) for a patient to survive up to 30 years old. The cost to manage related hematopoietic stem cell transplantation (HSCT) for patients aged 1 to 19 years was 80 700 to 574 000 THB per quality-adjusted life years (QALY) gained. The cost management of unrelated HSCT for patients aged 1 to 17 years was 209 000 to 3 270 000 THB per QALY gained (US$1 = 34 THB).[6]

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Table 1. Demographic and clinical characteristics of the study participants.

	PND (N = 21)	Non PND (N = 85)	*P*-value
TDT, n (%)	16 (76.19)	69 (81.20)	.612
NTDT, n (%)	5 (23.81)	16 (18.80)	
Weight for age *Z* score (mean, IQR)	0.16 (−0.57 to 0.76)	−0.09 (−0.91 to 0.76)	.201
Height for age *Z* score (mean, IQR)	0.39 (0.08 to 0.68)	−0.11 (−1.13 to 0.68)	***.018***
Gestational age at first ANC, week (range)	8 weeks (median) (4-16)	8 weeks (median) (3-28), missing data = 1	.356
Age at diagnosis for thalassemia, month (range)	6 months (median) (prenatal-48 months)	15 months (median) (1-144 months)	***.000***
The parent's known preconception risk for thalassemia	14 (66.67)	12 (14.12)	***≤.001***

In Thailand, the National Health Security Office (NHSO) has implemented a national strategic plan to prevent and control new cases of thalassemia since 2014. In the first step, the method proposed the couples are tested early during antenatal care (ANC) for Hb typing by a blood test. If the tests identify the risk of possible thalassemia in a fetus, the provider will give counseling for prenatal diagnosis (PND). Thailand uses the amniocentesis technique to PND at gestational age 14 to 20 weeks and terminates the pregnancy if the fetus is diagnosed with TDT. The cost of the PND process is reimbursed from the universal coverage insurance scheme.[7]

This study was retrospectively analyzed the data of thalassemia patients and their families to elucidate the history of antenatal care, including prenatal diagnosis and treatment of thalassemia postnatally. The study's objectives are to evaluate the clinical outcome of transfusion-dependent thalassemia (TDT) patients who received a PND to assess the reason for continuing a pregnancy. However, prenatal diagnosis was abnormal, and to evaluate the reasons why not performing PND in non PND thalassemia patients.

Methods

The study was performed at the Division of Hematology-Oncology, Department of Pediatrics, Faculty of Medicine, King Chulalongkorn Memorial Hospital (KCMH) from October 2019 to February 2020. Each enrolled participant was reviewed electrical medical records (EMR) and collected the data by self-reported questionnaire. We reviewed EMR about Demographic data, and thalassemia disease information was collected: age at diagnosis, weight for age, height for age, hemoglobin typing result, and treatment received. The questionnaire gave the participant's parents to collect the data about prenatal history, thalassemia status in their sibling, gestational age at first ANC visit, the reason for not did PND, gestational age at PND, and the reason for continuing pregnancy although abnormal PND.

Statistical Analysis

The participant's demographic data are presented as means (SD), medians (range), or percentages. An independent *t*-test was used to compare continuous data. We collected the data composed of weight for age *Z*-score, height for age *Z*-score, gestational age at first ANC and age at diagnosis of thalassemia. A Chi-square test was used to compare categorical variables between the groups. The data composed of the parent's known preconception that the fetus was at risk for developing thalassemia. All analyses were performed using SPSS, Version 21. The level of significance was set at .05 for all comparisons.

Ethical Approval and Informed Consent

The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand according to the ethics principles of the Declaration of Helsinki and the Belmont Report (reference number: IRB 460/62). Informed consent was obtained from the children themselves as well as their parents or legal guardians before engaging in the study.

Results

One hundred and six thalassemia participants (53 males and 53 females), with a median age of 8.5 years (IQR 8.00), were enrolled in the study. The demographic data are shown in Table 1, and Hemoglobin typing in the TDT group and the non-TDT group is shown in Figure 1. Twenty-one participants (19.8%) were prenatally diagnosed with thalassemia, with a median age of 8 years

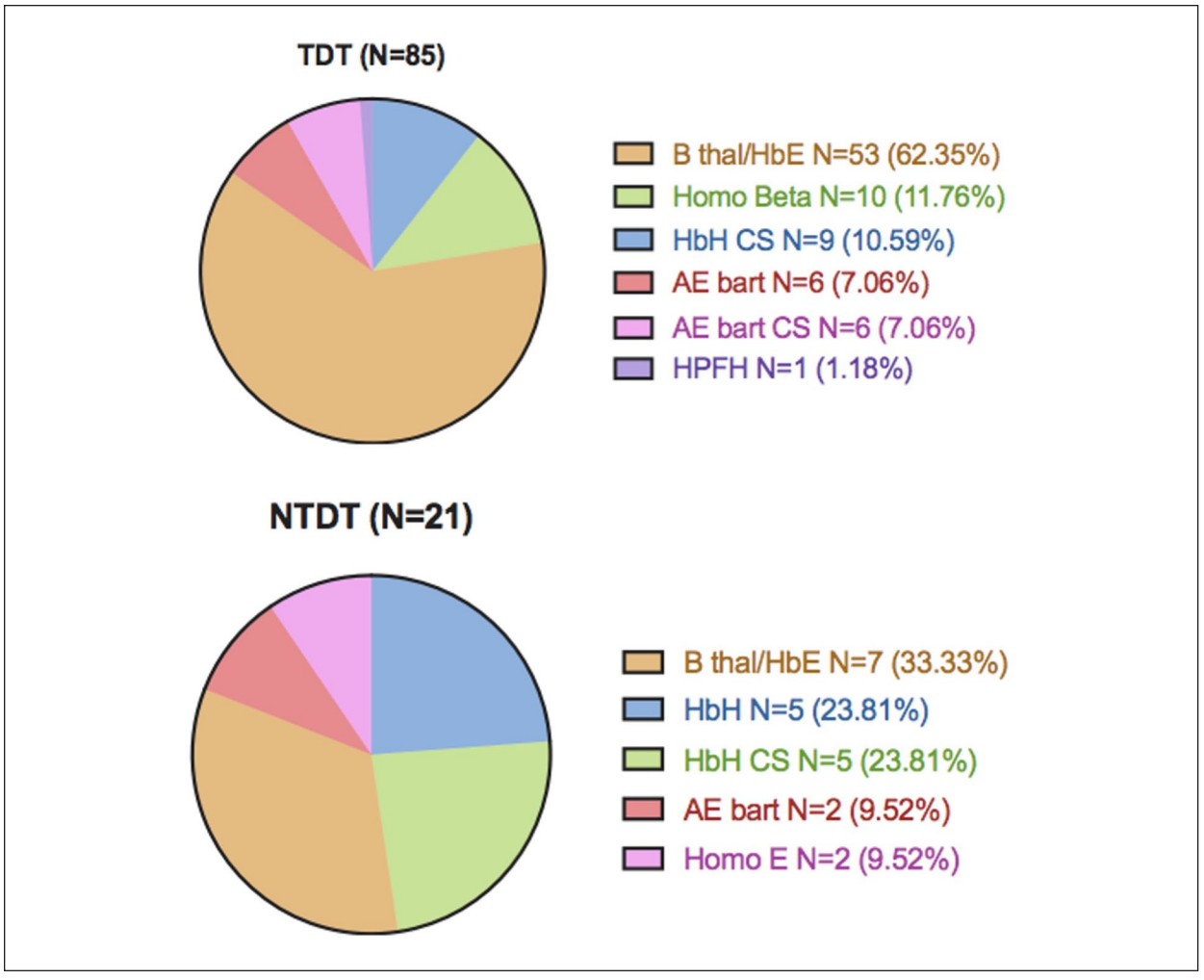

Figure 1. Hemoglobin typing in enrolled patients.

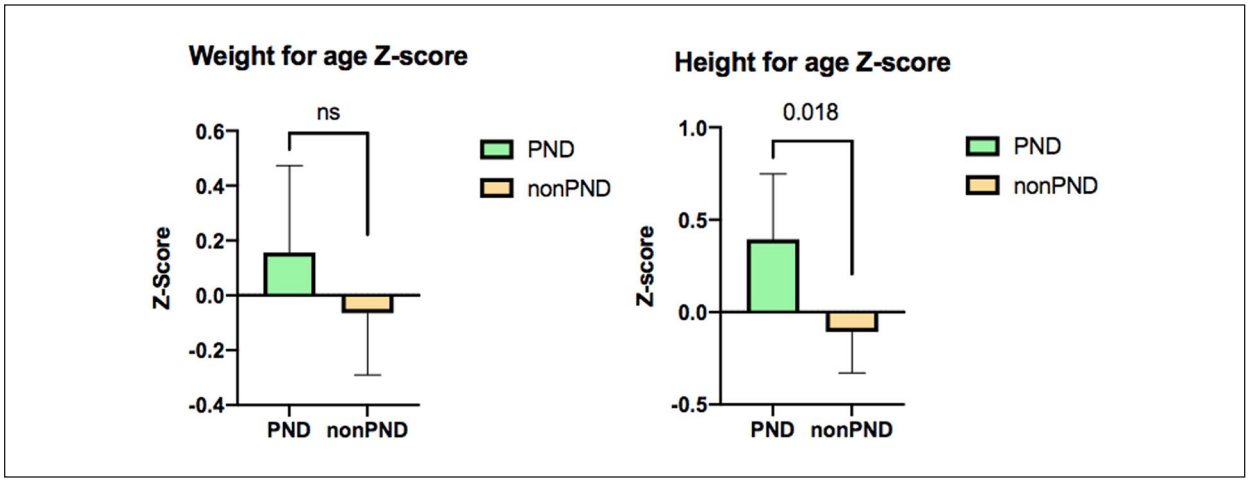

Figure 2. *Z*-score of weight for age and height for age in PND and non-PND groups.

(IQR 9.00), 16 were diagnosed with transfusion-dependence thalassemia (TDT), and 5 participants were diagnosed with non-TDT. Another 80.2% did not prenatally diagnose, with a median age of 9 years (IQR 8.00). For diagnosis in the PND group median age at diagnosis was 6 months, and non-PND group, the median age at diagnosis was15 months. There were statistically significant in early diagnosis TDT ($P < .001$). The participants' measurements of weight for age *Z*-score and height for age *Z*-score are shown in Table 1. The PND group's height for age *Z*-score is significantly higher than the non-PND group ($P = .018$), as shown in Figure 2. In contrast, the weight for age *Z*-score is not quite different between the 2 groups.

Sixty-six percent of the parents in the PND group knew that their child was at risk for developing thalassemia before conception compared to 14.2% in the non-PND group.

Some of the parents who underwent PND and had an abnormal result still wanted to continue their pregnancy. The most common reason to continue the pregnancy was the parents' willingness to have a child despite knowing that the child will require lifelong transfusion therapy (7 couples, 33%), followed by a refusal to terminate the pregnancy due to their belief/religion (28.5%), had false normal result (28.5%), and/or the result showed that the disease was mild (10%). Eight PND results showed benign conditions or normal results. Still, they were subsequently diagnosed with beta-thal/HbE in 6 participants, Persistence of Fetal Hemoglobin (HPFH) in 1 participant, and AE Bart disease in 1 participant. Four out of 8 participants are currently receiving regular transfusion therapy.

There are many reasons why couples do not get a PND. The most common obstacle was care providers did not recommend doing a PND in 58 couples (68.24%). Fifteen couples (17.64%) refused to do PND, and 7 couples (8.24%) had too late gestational age to have a PND.

Generally, birth control in thalassemia parents is temporary contraception (51 families, 48.11%), whereas 20.75% (22 families) used permanent contraception, 16.03% (17 families) did not use any contraception, and 16.03% (17 families) were divorced.

Discussion

In recent years have a review article documented that short stature is common in children with transfusion-dependent thalassemia. Many factors have been implicated in growth retardation: chronic anemia, transfusion-related iron overload,[8,9] and chelation toxicity. Other contributing factors include hypothyroidism, hypogonadism, GH deficiency/insufficiency, chronic liver disease, undernutrition, and psychosocial stress.[10]

But our study found that early diagnosis of TDT in the PND group significantly resulted in superior height outcome measure by height for age *Z*-score. This group had earlier receive a blood transfusion to cause no growth retardation from chronic anemia.[11] But in weight outcome had more factors such as parenting, feeding, and temperament, etc.

It is interesting that TDT's parents still use temporary contraception because they are willing to have another child, and they refuse abortion.

Our study found 28.5% of false normal PND results. The inaccurate PND results occurred because the procedure was not done by a fully comprehensive molecular testing, resulting in a falsely normal or mild result.

Most of our thalassemia participants were born without PND recommendations. The biggest reason for not having a PND is that the "doctors do not recommend it," which corroborates the findings from a previous study conducted in Thailand.[7] Since 2014, PND became available for free in the national health care program, making it more accessible to risk couples. Thus, hemoglobin typing and polymerase chain reaction (PCR) analysis for alpha-thalassemia were performed in most counseled couples.

Family counseling at the Department of Obstetrics and Gynecology, KCMH, during 2016 to 2017. A total of 210 risk couples were counseled. If the fetus has a possibility of having thalassemia major, the risk couples were sent to have second counseling for PND within a timely manner. Only 2 out of 100 risk couples refused to have PND. A review of unpublished data of a PND provider at KCMH found that the ratio of PNDs was higher than this study conducted on our pediatric patients. This conflicting finding may result from the transference of most of the patients from other centers to KCMH.

Limitation

This study was a cross-sectional study, most of our participants referred from outside hospitals, so some data was recall bias from the questionnaire and incomplete data. And this study was a single-center study.

Conclusion

PND is promoted to prevent new cases of thalassemia and its complication. Even though the result of PND was abnormal, yet the risk couples continued with their pregnancy. PND leads to earlier diagnosis and better growth outcomes. Currently, it is easier for risk couples to access PND. However, the problem lies with both the obstetrician and pediatrician on how to screen for thalassemia and family planning to assist the spouses in deciding whether to have PND or not.

Author Contributions

NA and PT involved in patients' care, collected, analyzed, interpreted the patient's data and was a major contributor in writing the manuscript; NC involved in collected, analyzed and interpreted the patient's data; SL, HP, KC and DS involved in patients' care and collected the patient's data. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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