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ASSOCIATION OF SHINE AND LAL INDEX β-THALASSEMIA TRAIT SCREENING RESULTS WITH ANAEMIA AND LOW BIRTH WEIGHT

Susanti[1], Muhammad Miftahussurur [2], Dominicus Husada[3], Woro Setia Ningtyas[1].
[1]Midwifery Study Programme, Faculty of Medicine, Universitas Airlangga
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga
[3]Department of Pediatric, Faculty of Medicine Universitas Airlangga
Email: susanti-2022@fk.unair.ac.id

ABSTRACT

Beta thalassemia trait are more likely to have anemia which leading to intrauterine hypoxia and adverse uterine conditions. Adverse intrauterine environment has been shown to have a significant impact on the risk of low birth weight. Therefore, this study aims to investigate association between Shine and Lal index β-thalassemia trait screening results with anaemia and lowbirth weight. A retrospective study design was conducted based on medical records of mothers and their infants born in 2022 at a regional hospital, in East Nusa Tenggara. The inclusion criteria were being live birth, singleton births and gestational age >28 weeks. Mothers didn't have complete records were excluded from study. Analysis uses chi-square test to evaluate the relationship between dependent and independent variables, This study identified 738 eligible samples. The incidence of suspected β-thalassemia trait according Shine and Lal Index was about 42.5%. There is a significant relationship between Shine and Lal β-thalassemia trait screening results with maternal anaemia and no relationship between Shine and Lal index β-thalassemia trait screening results and LBW.

Keywords

Anaemia, beta thalassemia trait, low birth weight, newborn

INTRODUCTION

Thalassemia is a genetic disease caused by red blood cell abnormalities in which the main hemoglobin-forming α- or β-globin chains are partially formed or absent altogether (Maskoen et al. 2019). The genetic disorder in thalassemia causes the body to only produce a small amount of Hb and red blood cells (El-Shanshory et al. 2021). Beta-thalassemia is one of the major types of thalassemia and results from decreased production of beta-globin (β-globin) chains. Based on the severity, thalassemia is divided into severe thalassemia (thalassemia major), thalassemia intermedia and asymptomatic thalassemia (thalassemia minor/ thalassemia trait) (Zhang, Yan, and Zeng 2018).

Moderate and severe thalassemia is usually diagnosed in childhood because symptoms usually appear during the first two years of a child's life. Meanwhile, people with mild thalassemia may be diagnosed after routine blood tests show that they have anemia. In contrast to β thalassemia, α thalassemia trait cannot be diagnosed in adults without genetic testing and is, therefore, highly underdiagnosed (Mettananda et al. 2018).

However, these thalassemic patients are prone to a variety of complications, including increased risk of cirrhosis, heart failure, and endocrinopathies, while ineffective erythropoiesis and hemolysis contribute to multiple complications,

including splenomegaly, extramedullary hematopoiesis, pulmonary hypertension, and thrombosis (Sayani and Kwiatkowski 2015). Thalassaemia in pregnancy may not have life-threatening symptoms, but the pregnancy outcome still requires attention (Adler, Wainstock, and Sheiner 2021).

Indonesia is located along the "thalassemia belt," where approximately 3.0 to 10.0 percent of the population carries β-thalassemia (Wahidiyat et al. 2022). In developed areas, thalassemia genetic screening is considered a routine prenatal examination, but not in most developing areas in Indonesia (Setiawan, Firmansyah, and Richard 2023). Awareness of carrier testing in hospitals and laboratories remains very low. Even families who have children with thalassaemia do not perform genetic testing. The strongest reason given by the family besides lack of knowledge about thalassemia, was the cost of the test, which is expensive and not covered by health insurance (Setiawan, Ediati, and Winarni 2017).

The diagnosis of β thalassemia is based on the clinical picture, complete blood count, and hemoglobin electrophoresis (Hernaningsih et al. 2022). Currently, several calculation formulas have been developed for thalassemia detection, including the Mentzer index (MCV/RBC), Srivastava index (MCH/RBC), Shine&Lal index (MCVxMCVxMCH/100) and any others. The Shine&Lal index is very helpful in initial screening of β-thalassemia trait, because this index confirms the presence of mutations in CD-26 and IVS1nt5 which are common mutations in Indonesia. The Shine&Lal index may be a useful predictor for thalassemia carrier screening in resource-limited settings where molecular methods are not readily available. The Shine & Lal index < 1530 could be used to predict all beta-thalassemia trait. (Maskoen et al. 2019, Noulsri et al. 2023)

However, more data is needed about the impact of β-thalassemia trait status on pregnancy outcomes. Carrying β thalassemia can increase the risk of LBW minimally but significantly, but does not increase the rate of bad outcomes in the mother (Charoenboon et al. 2016). Mothers with β-thalassemia trait are more likely to have anemia (Adler, Wainstock, and Sheiner 2021). Maternal anemia leading to intrauterine hypoxia and adverse uterine conditions (Kaplan et al. 2021). The intrauterine environment has been shown to significantly affect long-term outcomes for the fetus. Thalassemia in parents, can increase the risk of premature birth and low birth weight in newborns, and the risk may be higher in newborns whose mothers and fathers suffer from β-thalassemia(Huang et al. 2019).

Low birth weight has been defined by the World Health Organization (WHO) as a baby with a birth weight of less than 2,500 grams, regardless of gestational age, measured after birth, ideally within the first hours of life (WHO 2023). More than 80% of neonatal deaths worldwide are due to low birth weight (Blencowe et al. 2019). According to the Indonesian Demographic and Health Survey 2021, low birth weight (LBW) is considered as the most important predictor of neonatal mortality, more than 34.5% of neonatal mortality is caused by LBW (Kemenkes RI. 2021). At least 1,074 neonates died in eastern Indonesia, particularly in East Nusa Tenggara more than 25% of neonates died due to LBW.

In general, women who are carrier of β-thalassemia usually have no symptoms and do not experience anemia and can tolerate the hematological changes caused by pregnancy well. Research on the effect of β-thalassemia traits on pregnancy outcomes including low birth weight is still very limited. The varying availability and quality of LBW data across countries makes it difficult to investigate association between β-thalassemia trait and LBW, so improved quantity and quality is needed.

The high incidence of LBW and limited screening for β-thalassemia carriers in South Central Timor district has made researchers to conduct a study on the risk of suspect of β-thalassemia trait for the incidence of LBW in South Central Timor district. In particular, the risk of β-thalassemia trait in LBW, as far as researchers have observed, no research has evaluated the relationship between beta thalassemia trait and LBW in Indonesia. This study aims to determine the relationship between suspected β-thalassemia trait using Shine and Lal index with maternal anemia and low birth weight.

METHOD

A hospital-based retrospective case-control study was conducted at Soe Hospital, South Central Timor District. All registered deliveries from January to December 2022 were used as sample population with a total of 1163. The minimum sample size was determined using a proportion difference approach with the assumption of a 95 % confidence level ($Z\alpha/2 = 1.96$), 80 % power ($Z\beta = 0.84$) obtained a minimum sample size is 113.

There were a total of 738 eligible samples by using total sampling technique. Women who gave live births, singleton births, gestational age >28 weeks were included from this study. Women didn't have complete records were excluded from study.

Maternal characteristics factors (i.e., maternal age, parity, interpregnancy interval, educational level and occupation), suspected thalassemia β trait was the exposure/independent variable. Maternal anaemia and low birth weight was the outcome/dependent variable.

The data were obtained from the medical records on mothers at childbirth was entered into a data collection sheet. The data sheet included the following information: maternal socio demographic and obstetrics information including age, educational level, occupation, parity and pregnancy interval and illness during pregnancy. Information on infants was infant's birth weight.

Suspected beta thalassaemia trait are calculated and categorised using the haematological index Shine&Lal index with the formula (MCV) x (MCV) x (MCH) /100, with suspected beta thalassaemia trait defined as <1530. Haemoglobin (Hb) level on admission to hospital before delivery is a sign of anaemia. The components of the complete blood count, were from laboratory test results in medical records.

Ethical permitted letter number 91/EC/KEPK/FKUA/2023 was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Airlangga, Surabaya. Analysis uses chi-square test to evaluate the relationship between dependent and independent variables. Statistical tests were considered significant at a p value of less than 0.05.

RESULTS

Based on Table 1 below, based on maternal characteristics, as many as 71.0% mothers aged 20-35 years. There was multiparous 59.3%, pregnancy interval less than 2 years was more common in this study. As many as 40.9% respondents with high-school education. Regarding the occupation, 80.6% mothers are housewife.

Table 1- The maternal characteristics.

Variable	Category	Frequency (n)	Percentage (%)
Maternal Age	<20	38	5.1
	20-35	524	71.0
	>35	176	23.8
Parity	Primiparous	292	39.6
	Multiparous	364	59.3
	Grandemultiparous	82	11.1
Pregnancy interval	< 2 years	342	46.3
	2-5 years	269	36.4
	>5 years	127	17.2
Education	Illiterate	16	2.2
	Primary	275	37.3
	High-school	302	40.9
	University	145	19.6
Occupation	Employed	143	19.4
	Housewife	595	80.6
Suspected β - Thalassemia trait	Yes	314	42.5
	No	424	57.5
Low Birth Weight	Yes	123	16.7
	No	615	83.3

There was 42.5% suspected β thalassemia trait according Shine&Lal index. As many as 16.7% respondents were gave birth to low-birth-weight babies.

Table 2 Association of Pregnancy Outcomes with Suspected β-Thalassemia Trait

Variable	Suspected β-Thalassemia trait		Total	P value
	Yes	No		

Maternal Anaemia				
Severe anemia	13 (4.1)	3 (0.7)	16 (2.2)	**<0,001**
Moderate anemia	127 (40.4)	35 (8.3)	162 (22.0)	
Mild anemia	63 (20.1)	57 (13.4)	120 (16.3)	
Not anemic	111 (35.4)	329 (77.6)	440 (59.6)	
Low Birth Weight				
Yes	57 (46.3)	257 (41.8)	314 (42.5)	**0,405**
No	66 (53.7)	358 (58.2)	424 (57.5)	

Table 2 shows that a significant association between maternal anemia and thalassemia β trait (p<0.001). As many as 46.3% of the women who had thalassemia β trait were gave birth to low-birth-weight babies. This study found no association between thalassemia β trait and LBW (p=0.405).

Figure 1 Distribution of Haemoglobin Level with β Thalassemia Trait in Pregnancy

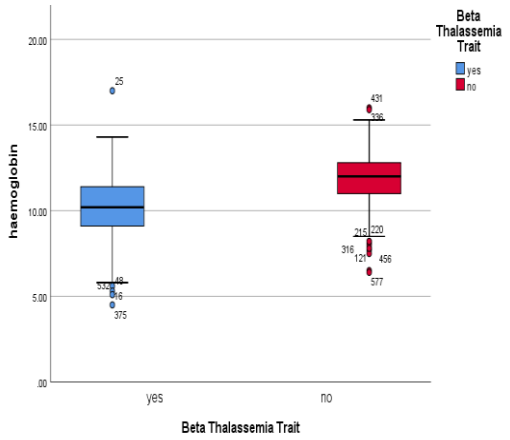

Figure 1 shows distribution of haemoglobin level with suspected β thalassemia trait.

DISCUSSION

There is a significant association between maternal anemia and thalassemia β trait in this study. This is consistent with the study by Adler, Wainstock, and Sheiner, mothers with β-thalassemia trait are more likely to have anemia (Adler, Wainstock, and Sheiner 2021). Women with the beta-thalassemia trait have limited production of beta-globin chains and are associated with hematologic disorders such as small red blood cell size (mean red blood cell volume) and decreased hemoglobin levels (mean red blood cell count) (Bharti et al. 2020). In theory, a 30% increase in red blood cell volume or a 40% increase in total blood volume (Cunningham et al. 2018) during pregnancy may be problematic in women with the β-thalassemia trait (Ruangvutilert et al. 2023).

Causes of anaemia in pregnancy include nutritional deficiencies, parasitic and bacterial infections, and congenital disorders such as thalassaemia. However, the most common cause of anaemia in pregnancy is iron deficiency. Regardless of whether there is iron deficiency, mothers with haemoglobin levels below the WHO standard (11.0 g%) are classified as having anaemia(Breymann 2015). Anaemia in pregnancy can result in disruption of the transfer of haemoglobin to the fetus through the placenta as a source of nutrition for the fetus(Shanty, Amalia, and Utomo 2023)

Thalassemia β trait was not associated with LBW incidence in this study. Mothers with β thalassemia trait did not have a tendency to give birth to LBW. This is consistent with the study by Kasparek(Hanprasertpong et al. 2013) and Barrett(Kemthong et al. 2016), who explained that the condition of thalassemia β trait did not affect the risk of IUGR and preterm birth, which are manifestations of LBW. This may be because the condition of thalassemia β trait is a genetic trait. The disease does not develop into a more severe form of thalassemia requiring medical treatment.

Although it is generally known that anemia in pregnancy is a significant risk factor for adverse maternal and fetal outcomes, the results of previous studies on the effect of the β-thalassemia trait on pregnancy have been inconsistent. A study showed an increased risk of adverse pregnancy outcomes (Ruangvutilert et al. 2023), while other studies could not confirm this Hanprasertpong (Hanprasertpong et al. 2013). Kasparek showed that trait thalassemia β increased

maternal risk but did not increase adverse neonatal outcomes (Kasparek et al. 2021). Mothers with the β-thalassemia trait are usually asymptomatic, do not have anemia, and have a good tolerance for hematology changes due to pregnancy (Charoenboon et al. 2016). It is unclear whether these women cope well with such dramatic changes, and whether beta thalassemia trait increases the rate of adverse pregnancy outcomes. To our knowledge, there is limited research on the effect of thalassemia traits on pregnancy outcomes(Charoenboon et al. 2016).

Clinical features in thalassemia carriers range from almost asymptomatic to severe anemia requiring lifelong blood transfusions. Ideally, prenatal screening should be used to identify couples with thalassemia who are at risk of having a child with thalassemia major. This strategy is a control measure aimed at reducing the incidence of new affected neonates. Couples with a family history of thalassemia planning to have a child are advised to undergo hemoglobinopathy screening followed by appropriate genetic counseling (Barrett, Saminathan, and Choolani 2017).

Limitations of this study include a retrospective approach in which some records contained missing or not fully reliable data. The results of prenatal blood tests were unknown in both groups, a complete blood test was performed at the end of pregnancy. Recording of blood test results in early pregnancy varies; most pregnant women do not have complete blood tests in early pregnancy due to limited resources at health facilities. Therefore, the condition at the beginning of pregnancy cannot be known with certainty.

CONCLUSIONS

This study provided evidence that suspected thalassemia β trait does not increased risk of low birth weight. Further studies and pregnancy registries should be organized and analyzed to establish guidelines for this important period of life for women with thalassemia.

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