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MATERNAL-FETAL MEDICINE

Pregnancy outcomes among women with beta-thalassemia trait

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Abstract
Objective To compare the obstetric outcomes between pregnant women affected by beta-thalassemia trait and normal controls.
Methods A retrospective cohort study was conducted on singleton pregnant women complicated by beta-thalassemia trait and normal controls, randomly selected with the controls-to-case ratio of 2:1. All were low-risk pregnancies without underlying medical diseases and fetal anomalies. The pregnancies undergoing invasive prenatal diagnosis were excluded.
Results A total of 597 pregnant women with beta-thalassemia trait and 1194 controls were recruited. Baseline characteristics and maternal outcomes in the two groups were similar, except that hemoglobin levels were slightly lower in the study group. The prevalence of small for gestational age and preterm birth tended to be higher in the study group but not reached the significant levels but the rate of low birth weight was significantly higher in the study group (relative risk 1.25; 95 % CI 1.00–1.57). Additionally, abortion rate was also significantly higher in the study group (relative risk 3.25; 95 % CI 1.35–7.80).
Conclusion Beta-thalassemia trait could minimally, but significantly, increase risk of low birth weight but did not increase rates of maternal adverse outcomes.

Keywords Beta-thalassemia · Pregnancy · Outcomes · Trait

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Introduction

Thalassemia is a common genetic disorder in Asia. It is not only an important public health problem but also a socio-economic problem of many countries in the region [1]. In our pregnant population, northern part of Thailand, overall prevalence of thalassemia trait may be as high as 25.4 % which can be classified as follows: alpha-thalassemia-1 (SEA type) trait 6.6 %, beta-thalassemia trait 3.7 %, hemoglobin E trait 11.6 %, and homozygous HbE 0.8 % [2]. Fertility is usually compromised in women with thalassemia disease. However, pregnancies complicated with thalassemia disease can be occasionally encountered and they were reported to have a higher risk of adverse obstetric outcomes, such as preterm birth and small for gestational age [3–5]. Nevertheless, little is known regarding the effects of thalassemia carrier status on the pregnancy outcomes. In general, women with beta-thalassemia trait are usually asymptomatic and not anemic and can well tolerate pregnancy-induced hematological changes. Women with beta-thalassemia trait have some limitations in production of beta-globin chain and are associated with subtle hematologic disorders such as small size of red blood cells (mean corpuscular volume) [6] and decreased hemoglobin level (mean corpuscular hemoglobin) [7]. Theoretically, considerable changes such as a 30 % increase in red blood cell volume or 40 % increase in total blood volume [8] during pregnancy may possibly be problematic among women with beta-thalassemia trait. It is unclear whether or not those women can cope well with such dramatic changes and whether beta-thalassemia trait increases rates of adverse pregnancy outcomes or not. To the best of our knowledge, the studies on effects of thalassemia traits on pregnancy outcomes are very limited. In 2013, Hanprasertpong et al. [9] studied on obstetric

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outcomes of 739 women complicated by thalassemia trait, compared to 799 normal controls and found that thalassemia trait increases risk of preeclampsia (relative risk 1.73; 95 % CI 1.01–3.00). However, the study included beta-thalassemia trait, alpha-thalassemia-1 trait and HbE trait, without subgroup analysis. Because little had been known about the impact of beta-thalassemia trait on pregnancy outcomes and the prevalence was high in our population, we conducted this study to compare the pregnancy outcomes such as preterm birth, small for gestational age and preeclampsia between pregnant women with beta-thalassemia trait and normal controls.

Materials and methods

This retrospective cohort study was conducted at Maharaj Nakorn Chiang Mai hospital, Chiang Mai University with ethical approval by institute review boards. The prospective database of the maternal–fetal medicine unit between January 2003 and December 2013 was assessed to identify the records which met the following criteria: (1) pregnant women with beta-thalassemia trait diagnosed during or before pregnancy based on hemoglobin typing or DNA analysis, (2) singleton pregnancies, (3) attending prenatal care clinic and delivery at Maharaj Nakorn Chiang Mai hospital, (4) no other medical or surgical conditions such as pregestational diabetes, chronic hypertension or anemia due to any causes, and (5) available data of the pregnancy outcomes. The control groups had the same inclusion criteria as the study group but had no carrier status of thalassemia/hemoglobinopathies. The controls were randomly selected with controls-to-case ratio of 2:1. The women undergoing invasive diagnostic procedures, i.e., chorionic villous sampling, amniocentesis, and cordocentesis, and pregnancies with fetal structural, chromosomal abnormalities, or fetal thalassemia disease were excluded from analysis.

The pregnant women in the two groups were taken standard care and followed up as low risk pregnancies at our antenatal clinics. Gestational age was established at the first visit, either by clinical estimation or by ultrasound in the first half of pregnancy. Hemoglobin levels were assessed at first visit and third trimester. Routine anomaly screening by ultrasound was performed at mid-pregnancy. Maternal records were reviewed for age, parity, gestational age, obstetric complications such as preeclampsia, gestational diabetes, antepartum or postpartum hemorrhage, and mode of delivery. Neonatal records were reviewed for Apgar scores, birth weight, small for gestational age, preterm birth, and low birth weight. The main outcomes were prevalence of preterm delivery, low birth weight (LBW), and small for gestational age (SGA). The secondary outcomes were the rates of stillbirth, spontaneous abortion, preeclampsia, antepartum/postpartum hemorrhage, cesarean delivery, low Apgar score at 1 and 5 min, urinary tract infection, and gestational diabetes mellitus (GDM). The main definitions used in this study were as follows: (1) Low birth weight: birth weight of <2500 g, (2) Preterm delivery: delivery before 37 complete weeks and >20 weeks, (3) small for gestational age (SGA): a fetus with birth weight of lower than the tenth percentile for gestational age, (4) Spontaneous abortion: spontaneous fetal loss at gestational age of 20 weeks or less, (5) Stillbirth: fetal death at >20 weeks of gestation, (6) Low Apgar scores at 1 and 5 min: the scores of <7 at 1 and 5 min after birth, (7) Preelcampsia: new onset of hypertension (>140/90 mmHg on at least 2 occasions at least 6 h apart) with proteinuria (>300 mg/24-h urine or >1 + urine dipstick), and (8) Gestational diabetes mellitus (GDM): diabetes mellitus first diagnosed during the current pregnancy based on the findings of at least 2 abnormal values of a 3-h glucose tolerance test.

Statistical analyses were performed using SPSS version 21.0 (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). Baseline data were presented as number (percentage) or mean (±standard deviation), as appropriate. Obstetric outcomes were compared between the women with beta-thalassemia trait and the control group using Chi-square test, as well as relative risks with 95 % confident interval. A p value <0.05 was considered statistically significant.

Results

During the study period, 597 women with beta-thalassemia trait met the inclusion criteria, classified as the study group and 1194 normal controls were randomly recruited in the control group. Most baseline characteristics, including maternal age, weight, and BMI, were comparable between the two groups as presented in Table 1. However, the number of prenatal visits in the study group was significantly higher than that in the control group (8.88 vs 7.85, respectively; $P < 0.001$). Similarly, the hemoglobin level in the study group was slightly but significantly lower than that in the control group (10.7 ± 1.9 vs 11.4 ± 1.7, respectively, $P = 0.001$). The abortion rate in the study group was significantly higher, 13 (2.2 %) vs 8 (0.7 %), $p = 0.005$, RR 3.25 (95 % CI 1.35–7.80).

Analyses of the pregnancy outcomes after excluding cases with abortion are as follows: There were no significant differences in the prevalence of most maternal and fetal outcomes such as preeclampsia, antepartum hemorrhage, postpartum hemorrhage, gestational diabetes mellitus, asymptomatic bacteriuria and peripartum infections, low Apgar scores at 1 and 5 min, and cesarean delivery, as

Table 1 Baseline characteristics of pregnant women with beta-thalassemia trait and controls

Baselines characteristics	Study group ($n = 597$)	Control group ($n = 1194$)	P value
Maternal age (years)	27.29 ± 5.08	27.27 ± 6.00	0.950[a]
Maternal BMI (Kg)	22.9 ± 3.7	22.8 ± 3.8	0.863[a]
Number of prenatal visits	8.58 ± 3.03	7.85 ± 4.53	<0.001[a]
Hemoglobin levels at first visit (g/dl)	10.7 ± 1.9	11.4 ± 1.7	0.001[a]
Parity: number (%) ($n = 1769$)[c]			0.089[b]
Nulliparity	336 (57.5 %)	631 (53.2 %)	
Multiparity	248 (42.5 %)	554 (46.8 %)	
Educational level			0.105[b]
High (university or more)	113 (18.9)	243 (20.4)	
Middle (secondary school)	311 (52.1)	594 (49.7)	
Low (primary school or less)	126 (21.1)	291 (24.4)	
Occupation			0.221[b]
Agriculture	19 (3.3)	49 (4.2)	
Commercial	59 (10.2)	102 (8.8)	
Employee	314 (54.4)	623 (53.9)	
Government officer	16 (2.8)	47 (4.1)	
Private business	12 (2.1)	10 (0.9)	
Housewife	130 (22.5)	274 (23.7)	
Others	27 (4.7)	51 (4.4)	

[a] Student's T test

[b] Chi square test

[c] There were some missing data of parity

Table 2 Comparisons of the obstetric outcomes between the two groups

Outcome	Study group[a] ($n = 584$)	Control group[a] ($n = 1186$)	P value	Relative risk (95 % CI)
Preterm birth	85 (15.0)	165 (13.9)	0.539	1.08 (0.85–1.37)
Small for gestational age	55 (9.4)	85 (7.2)	0.099	1.31 (0.95–1.82)
Low birth weight	105 (18.0)	170 (14.3)	0.047	1.25 (1.004–1.565)
Macrosomia	67 (11.5)	147 (12.4)	0.576	0.93 (0.71–1.21)
Gestational diabetes mellitus	46 (7.9)	88 (7.4)	0.733	1.06 (0.75–1.50)
Preeclampsia	37 (6.3)	82 (6.9)	0.648	0.92 (0.63–1.33)
Stillbirth	10 (1.7)	21 (1.8)	0.932	0.97 (0.46–2.04)
Apgar score <7 at 1 min	38 (6.5)	80 (6.8)	0.850	0.97 (0.66–1.40)
Apgar score <7 at 5 min	14 (2.4)	30 (2.5)	0.869	0.95 (0.51–1.78)
Cesarean delivery	92 (15.8)	165 (13.9)	0.301	1.13 (0.90–1.43)
Asymptomatic bacteriuria	15 (2.5)	32 (2.7)	0.834	0.94 (0.51–1.72)
Peripartum infection[b]	21 (3.5)	39 (3.3)	0.781	1.07 (0.64–1.81)
Antepartum hemorrhage	9 (1.5)	22 (1.8)	0.608	0.82 (0.38–1.77)
Postpartum hemorrhage	21 (3.5)	35 (2.9)	0.502	1.20 (0.71–2.04)

[a] Values are given as number (percentage)

[b] Including chorioamnionitis, postpartum metritis, and wound infections

presented in Table 2. The prevalence of low birth weight fetuses was significantly higher in the study group (18.0 vs 14.3 %, $p = 0.047$, RR 1.25, 95 % CI 1.004–1.565). Similarly, the mean gestational age at birth in the study group was slightly, but significantly, lower than that in the control group, (37.58 ± 3.63 vs 38.12 ± 32.7 weeks, respectively; $P < 0.001$). Likewise, the mean birth weight in the study group was significantly lower (2791 ± 643 vs 2949 ± 539 gm; $P < 0.001$). Note that the rates of preterm birth and small for gestational age tended to be increased in the study group, but the differences did not reach significant levels.

Discussion

This study suggests that non-anemic beta-thalassemia trait not significantly increase risk of common maternal complications such as preeclampsia, gestational diabetes mellitus, obstetric hemorrhage, infectious morbidities and cesarean delivery. Nevertheless, beta-thalassemia trait was significantly associated with an increased rate of fetuses with low birth weight. Interestingly, the rates of preterm delivery and small for gestational age had a tendency to be increased but did not reach a significant level whereas low birth weight, which is primarily contributed by both preterm delivery and small for gestational age, was significantly increased with beta-thalassemia trait, possibly associated with the lower hemoglobin levels as seen in the study group. These findings indicated that beta-thalassemia trait might probably have minimal effect on both preterm birth and small for gestational age, which the study had not enough power to express. Therefore, further studies with larger sample size are needed to answer this issue. Nevertheless, such a minimal increase in the prevalence of low birth weight with a relative risk of 1.25 may be unlikely to have overall clinical impact as signified by no significant difference in rates of other outcomes like low Apgar Scores, stillbirth, cesarean delivery, obstetric hemorrhage, preeclampsia, etc. Additionally, abortion rate was higher in the women with beta-thalassemia trait when compared to the normal controls. However, the number of cases with abortion was too low with a wide range of 95 % CI of the relative risk. Therefore, such a relationship should be confirmed by further prospective studies.

Notably, the prevalence of preeclampsia in the women with beta-thalassemia trait was not significantly different from that in the controls, unlike the finding demonstrated by Hanprasertpong et al. [9], who reported a significant increase in the risk of preeclampsia in women with thalassemia traits. Presumably, such a finding might possibly be associated with other types of thalassemia traits, because their study group included women with several types of traits, i.e.: alpha-thalassemia-1, beta-thalassemia and hemoglobin E trait.

The strength of this study included (1) adequate sample size to gain power in differentiating rates of common adverse outcomes, (2) high homogeneity of the study population recruited from a single center, and (3) pregnancies with known potential confounders such as medical complications, undergoing invasive diagnosis like amniocentesis, as well as fetal anomalies were excluded. Limitations of this study included (1) The retrospective approach in which several records contained missing or not perfectly reliable data, (2) Selection error might have occurred during recruitment of the controls, as noted that the number of prenatal visits was significantly different. However, since the visit number was higher in the study group, which could lead to better outcomes, the conclusion of the worse outcomes associated with beta-thalassemia trait could not be changed, and (3) Postpartum hemoglobin levels of the two groups were not compared. Therefore, we could not evaluate the exact impact of the disorder on postpartum complications, though the prevalence of postpartum hemorrhage was not significantly different.

In conclusion, this study provided evidence that beta-thalassemia trait minimally increased risk of low birth weight and spontaneous abortion, whereas the prevalence of maternal complications were not significantly increased.

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Compliance with ethical standards

Conflict of interest No conflict of interest.

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