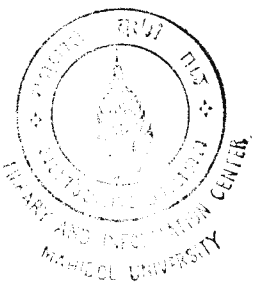

PREGNANCY OUTCOME OF THALASSEMIA

PARADEE CHOMPOOKAEW

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PARADEE CHOMPOOKAEW: PREGNANCY OUTCOME OF THALASSEMIA. THESIS ADVISOR: SURAPOL SUWANAGOOL M.D., F.A.C.P., JAYANTON PATUMANOND M.D., D.Sc., CHAMAIPORN TAWICHASRI, M.Sc., SOYSAANG SETHAVANICH, M.D. 133P. ISBN 974-665-002-5

A retrospective follow-up study was conducted to evaluate the pregnancy outcome of Thalassemia. The study subjects were pregnant women who were screened for Thalassemia at antenatal care clinic of the Mother and Child Hospital, Chiang Mai, between 1st December 1997 and 15th June 1999. The sample comprised of 13 cases of Thalassemia disease, 132 cases of Thalassemia trait, and 319 pregnant women without such conditions. The information were collected from antenatal care and delivery records. The hematocrit of women with Thalassemia trait and Thalassemia disease was 1.69% (95% CI = 1.03 to 2.35) and 3.45% (95 CI = 1.52 to 5.39) lower than that of women without the conditions. There were no differences in variable factors among women of all the three groups at the time of delivery. Puerperal infection in Thalassemia trait and Thalassemia disease was 2.98 (95%CI = 1.47 to 6.06) and 5.42 times (95%CI = 1.55 to 18.88) more likely. In women with Thalassemia disease, the chances of having a low birthweight infant was 9.26 times (95%CI = 2.92 to 29.35) more likely, the infant length was 1.85 cm (95%CI = 0.37 to 3.33) and the head circumference was 1.26 cm (95%CI = 0.39 to 2.12) shorter. Among infants who were born to women with Thalassemia trait, the chances of having fever within 7 days after birth was 1.65 times (95%CI = 1.09 to 2.50) more likely. Their hematocrit was 3.15% (95%CI = 1.69 to 4.62) less.

The results of the study indicated that surveillance of anemia and iron supplements should be more emphasized in antenatal care clinic to decrease anemia and infection among mothers and infants. Apart form the existing Thalassemia prevention and control campaign, women with Thalassemia trait should also receive more attention from health personnel.

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การศึกษาติดตามชนิดย้อนหลัง เพื่อศึกษาผลการตั้งครรภ์ของหญิงที่เป็นธาลัสซีเมีย ที่มารับบริการฝากครรภ์และคลอดที่โรงพยาบาลแม่และเด็ก จังหวัดเชียงใหม่ ระหว่างวันที่ 1 ธันวาคม พ.ศ. 2540 ถึง วันที่ 15 มิถุนายน พ.ศ. 2542 กลุ่มศึกษาเป็นหญิงตั้งครรภ์ที่ได้รับการตรวจคัดกรองการเป็นธาลัสซีเมีย และเป็นโรคเลือดธาลัสซีเมียจำนวน 13 ราย เป็นพาหะธาลัสซีเมียจำนวน 132 ราย และหญิงตั้งครรภ์อื่นๆ จำนวน 319 ราย รวบรวมข้อมูลจากแบบบันทึกการฝากครรภ์และบันทึกการคลอด ผลการศึกษาพบว่าหญิงที่เป็นพาหะธาลัสซีเมียและหญิงตั้งครรภ์ที่เป็นโรคเลือดธาลัสซีเมีย มีค่าความเข้มข้นของเม็ดเลือดแดงขณะตั้งครรภ์ ต่ำกว่าหญิงตั้งครรภ์ที่ไม่มีภาวะดังกล่าว 1.69% (95%CI = 1.03 ถึง 2.35) และ 3.45% (95%CI = 1.52 ถึง 5.39) ไม่พบความแตกต่างระหว่างหญิงตั้งครรภ์ทั้ง 3 กลุ่มขณะคลอด การติดเชื้อหลังคลอดของหญิงตั้งครรภ์ที่เป็นพาหะธาลัสซีเมียและหญิงตั้งครรภ์ที่เป็นโรคธาลัสซีเมีย สูงกว่า 2.98 เท่า (95%CI = 1.47 ถึง 6.06) และ 5.42 เท่า (95%CI = 1.55 ถึง 18.88) ทารกที่คลอดจากแม่ที่เป็นโรคเลือดธาลัสซีเมียมีโอกาสเป็นทารกน้ำหนักน้อย 9.26 เท่า (95%CI = 2.92 ถึง 29.35) ความยาวทารกน้อยกว่า 1.85 ซม. (95%CI = 0.37 ถึง 3.33) และความยาวเส้นรอบศีรษะน้อยกว่า 1.26 ซม. (95%CI = 0.39 ถึง 2.12) ทารกที่คลอดจากแม่ที่เป็นพาหะธาลัสซีเมียมีโอกาสพบอาการไข้ภายใน 7 วัน 1.65 เท่า (95%CI = 1.09 ถึง 2.50) และมีความเข้มข้นเม็ดเลือดแดงน้อยกว่า 3.15% (95%CI = 1.69 ถึง 4.62)

ผลการศึกษานี้ เป็นข้อบ่งชี้ว่าควรเพิ่มการเฝ้าระวังและเสริมธาตุเหล็กให้มารดาขณะตั้งครรภ์และคลอด เพื่อลดภาวะซีดและการติดเชื้อของมารดาและทารก และนอกจากการเร่งรัดโครงการควบคุมป้องกันธาลัสซีเมียแล้ว ยังควรพิจารณาให้ความสนใจแก่หญิงตั้งครรภ์ที่ตรวจพบว่าเป็นพาหะธาลัสซีเมียด้วย

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CHAPTER I

INTRODUCTION

Background

Thalassemias or Cooley's anemia was established since Hippocrates era. This is a genetically determined hemoglobinopathies those are characterized by impaired production of one or more of the normal globin peptide chains. It is transmitted by single recessive gene. The disease mostly occurs in Mediteranian eg., Greek, Italy, Africa and in Asia eg., China and Thailand. Worldwide prevalence of Thalassemia trait is about 240 million people (1).

In Thailand, Thalassemia is a chronic hereditary anemic disease that has the highest incidence and tends to increase every year (2). In Thai population, Thalassemia trait was probably 30 – 40% (18 – 24 million people) whereas prevalence of Thalassemia disease was 1% (600,000 people) for all over part of Thailand (3) (table 1).

Table 1 Prevalence of common hemoglobin abnormality in Thailand, classified by region (4)

Region	**alpha Thalassemia (%)**	**beta Thalassemia (%)**	**Hemoglobin E (%)**
North	30	9-10	8
Center	20-25	3	13-17
South	16	2-4	9-11
Northeast	20	2-6	32-36

Source: Laosombat V. Thalassemia.1998

Thalassemia screening for high-risk couples in northern part of Thailand demonstrated that Thalassemia trait pregnant women was 29.5% (5) and in Chiang Mai province was 30.5% (table2).

Table 2 Prevalence of Thalassemia in pregnant women at antenatal clinic (6,7)

Period	**Location**	**Number**	**Thalassemia**	**%**
Sep 1995 – Sep 1998	Maharaj hospital	12,145	3,708	30.53
Oct 1997 – Sep 1998	The Mother & Child Hospital	3,194	981	30.71

Thalassemia trait and Thalassemia disease pregnant women had more anemia than women without such conditions. The abnormal in globin chain synthesis, which is an important part of hemoglobin synthesis, may result in ineffective erythropoesis, hemolysis, and varying degrees of anemia (8).

World Health Organization (WHO) definition of anemia during pregnancy is hemoglobin level less than 11 gm/dl or hematocrit is less than 33% (9). Anemia during pregnancy causes high mortality and morbidity to mother and fetus eg. prematurity, low birth weight infant, high placental size and weight (8,10,11).

The purpose of this study is to identify effect of Thalassemia on pregnancy in Thai population. This study should benefit the health care providers to formulate improved quality of care for the Thalassemia pregnancy.

Objective

1. To study effects of Thalassemia on pregnancy
2. To study health status of newborns born to Thalassemia mother

Research Hypothesis

1. Pregnancy outcome of Thalassemia pregnancy is different from non-Thalassemia pregnancy.

2. Health status of newborn babies born to Thalassemia mother is different from the newborn babies born to non-Thalassemia mother.

Research variables

Independent variables

Pregnant women with underlying Thalassemia

Dependent variables

1. Effect on pregnancy: premature birth, toxemia of pregnancy, placental size and weight, anemia during pregnancy and puerperium infection.

2. Effect on newborn: low birth weight infant, still birth, neonatal hyperbilirubinemia, anemia of the newborn and infection of the newborn.

Confounding Variables

Maternal age, education level, marital status, antenatal care visit, HIV infection etc.

Definition of term

Thalassemia: The genetically determined hemoglobinopathies that are classified as Thalassemia are characterized by impaired production of one or more of the normal globin peptide chains (4).

Hemoglobinopathy: defined as abnormal hemoglobins characterized by the presence of both a biosynthetic defect and an abnormal structure (4).

Thalassemia disease: The Thalassemia constitutes a heterogeneous group of naturally occurring, inherited mutations characterized by abnormal globin gene function resulting in total absence or quantitative reduction of globin chain synthesis in human erythroid cells (4).

Thalassemia trait: The Thalassemia constitutes a heterogeneous group of naturally occurring, inherited mutations characterized by abnormal globin gene function resulting in partial absence or quantitative reduction of globin chain synthesis in human erythroid cells (4).

Anemia in pregnancy: anemia in pregnant women is defined as hemoglobin concentration less than 10 g/dl or hematocrit less than 33% during pregnancy (9).

Preeclampsia: The diagnosis of preeclampsia is based on blood pressure criteria, as well as proteinuria or edema or both. Blood pressure must increase by at least 30 mm Hg systolic or 15 mm. Hg diastolic (14).

Premature delivery: Premature delivery is defined as infants born before 37 weeks gestational or 253 days from the first day of the mother's last menstrual period (13).

Term infant: An infant born anytime after 37 completed (menstrual) weeks of pregnancy (13).

Puerperium infection: The standard definition of postpartum febrile morbidity is a temperature of 38.0° c (100.4° F) or higher on any 2 of the first 10 days postpartum, exclusive of the first 24 hours (13).

Stillbirth: Stillbirth is defined, none of the signs of life are present at or after birth (13).

Low birth weight infant: Newborn who has body weight obtained after birth less than 2,500 grams (15,16).

Neonatal anemia: Newborn who has hematocrit less than 30% in the first week or less than 40% in the next weeks. (16).

Hyperbilirubinemia: Conditions of increased bilirubin level to more than 12 mg./100ml.in premature birth, and 14 mg./100ml.in term infants (16,17).

Birth asphyxia: Newborn who has Apgar score of 7 or less after the first few minutes of life will be considered of having birth asphyxia (17).

CHAPTER II

LITERATURE REVIEWS

Information regarding pregnancy outcome in Thalassemia women were collected from a number of textbooks and research papers as the following areas:

1. Hematologic changes during pregnancy
2. Effect of Thalassemias on pregnancy
3. Thalassemias status in Thailand

1. Hematologic changes during pregnancy

Pregnancy induces many physiological changes in women. One of the most important changes is in hematologic system. The maternal blood volume increases markedly during pregnancy. Several studies of pregnant women showed that the average blood volume at or very near term is about 40 – 50 percent above their non-pregnant levels. Pregnancy-induced hypervolemia serves to meet the demands of the enlarged uterus with its greatly hypertrophied vascular system; to protect the mother, and in turn the fetus, against the deleterious effects of impaired venous return in the supine and erect positions. Maternal blood volume starts to increase during the first trimester, expands most rapidly during the second trimester, and then rises at a much slower rate during the third trimester to plateau during the last several weeks of pregnancy (18,19). Increased blood volume results from an increase in both plasma and erythrocytes. Although more plasma than erythrocytes is usually added to the maternal circulation, the increase in the volume of circulating erythrocytes is

considerable (20), averaging about 450 ml, or an increase of about 33 percent. Moderate erythoid hyperplasia is present in the bone marrow, and the reticulocyte count is elevated slightly during normal pregnancy. This is almost certainly due to a two to threefold increase in maternal plasma erythropoeitin levels. However, these result in slightly decrease in concentrations of hemoglobin and erythrocytes, as well as the hematocrit, during normal pregnancy. Consequently, whole blood viscosity decreases (21).

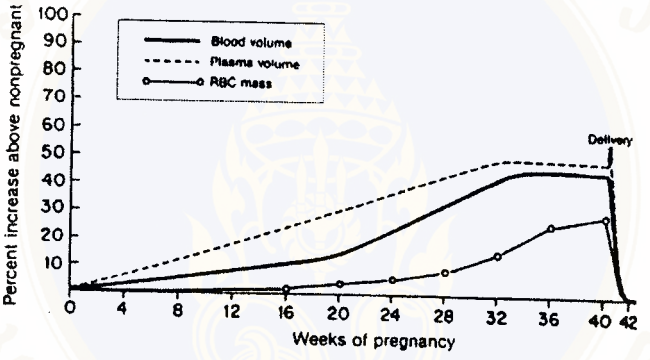

Figure 1 Blood volume changes during pregnancy.

Source: Cunning F.G. Willaim Obstetric, 1997.

In a well-controlled study in which iron was readily available to the mother for erythropoiesis, Pritchard and Hunt (1958) showed that the hemoglobin concentration at term averaged 12.5 g/dL; on only 6 percent was this below 11.0 g/dL. Thus in most women, a hemoglobin concentration below 11.0 g/dL, especially late in pregnancy, should be considered abnormal and usually due to iron deficiency rather than to hypervolemia of pregnancy (22).

The Centers for Disease Control (1989) defined anemia as less than 11 g/dL. in the first and third trimesters, and less than 10.5 g/dL. in the second trimester which total serum ferritin level not less than 12 μg/L (23).

The iron requirements in normal pregnancy is about 1000 mg. About 300 mg are actively transferred to the fetus and placenta and about 200 mg are lost through various normal routes of excretion. These are obligatory losses and occur even when the mother is iron deficient. The average increase in the total volume of circulating erythrocytes of about 450 mL during pregnancy, when iron is available, uses another 500 mg of iron, because 1 mL of normal erythrocytes contains 1.1 mg of iron. Practically, all of the iron for these purposes is used during the latter half of pregnancy. Therefore, the iron requirement becomes quite large during the second half of pregnancy, averaging 6 to 7 mg/day (24). Because this amount is not available from body stores in most women, the desired increase in maternal erythrocyte volume and hemoglobin mass will not develop unless exogenous iron is made available in adequate amounts. In the absence of added exogenous iron, the hemoglobin concentration and hematocrit fall appreciably as the maternal blood volume increases. Hemoglobin production in the fetus, however, will not be impaired, because the placenta obtains iron from the mother in amounts sufficient for the fetus to establish normal hemoglobin levels even when the mother has severe iron-deficiency anemia.

Table 3 Etiologies of Anemia in Pregnancy (8)

ACQUIRED
Iron – deficiency anemia
Anemia caused by acute blood loss
Anemia of inflammation of malignancy
Megaloblastic anemia
Acquired hemolytic anemia
Aplastic or hypoplastic anemia
HEREDITARY
Thalassemias
Sickle – cell hemoglobinopathies
Other hemoglobinopathies
Hereditary hemolytic anemias

Effects of anemia mainly depend on causes of anemia, for examples, newborns delivered from mother who have underlying disease eg. Thalassemias should have more impact than who delivered from normal pregnancy mother. One of assumption is that the impacts are not directly to effect of anemia itself but from complications of anemia to circulatory system, especially to vessels.

Studies about effects of anemia on pregnancy outcome are:

Mother

Complications during pregnancy

Many studies showed that pregnancy with hemoglobin level less than 9 mg/dL had high tendency of infection (25). Anemia is contributed to low immunity against infection (26), but no difference in terms of complications during pregnancy (27). Some studies also showed that pregnancy with high level of hemoglobin had high incidence of toxemia of pregnancy (28).

Abortion

Anemia during pregnancy is caused by low red blood cell production or high red blood cell destruction. It had definitely high correlation to spontaneous abortion, especially when hemoglobin level was less than 6 mg.% (14). In addition, other forms of anemia such as hemoglobinopathy as well as abnormality in fetus contributed to spontaneous abortion (26).

Weight gain during pregnancy

During pregnancy, mother would have many physiologic changes in responsible to fetal growth. Weight gain in the first trimester of pregnancy is not much, but it should increase about 0.4 – 0.5 kg/week afterwards (29). Underlying Thalassemias which had high tendency of hemolysis and anemia would have effected in carrying of nutrients and oxygen to maternal and fetal body and caused intrauterine growth retardation (8,30) and finally to poor weight gain during pregnancy.

Mode of delivery

The study in Hongkong showed that there was no difference in mode of delivery in normal pregnancy and pregnancy with hemoglobin less than 10 mg/dL (27).

Size and placental weight

According to the studies of maternal factors associated to placental size and weight, pregnancy with iron deficiency anemia would have statistically significant in placental size and placental to fetal weight ratio more than normal pregnancy (31,32). This adapted placental size to maternal anemia would increase oxygen supply to fetus (33).

Puerperium infection

Anemia is a risk factor for puerperium infection. This is due to low immunity against infections and low tolerance to severe blood loss (26,29).

Cord length

There was no study about relationship between anemic pregnancy and cord length. However, report of placental size and weight correlated to gestational age found that gestational age had high correlation to cord length ($p < 0.05$). The reason for this result is not clear (34).

Premature delivery

High correlation between low level hemoglobin during pregnancy and premature delivery was demonstrated in many previous studies. Risk of premature delivery was higher in very low level hemoglobin occurring at 5th and 8th month pregnancy (25, 33, 35, 36, 37). Some studies showed that both high and low level hemoglobin in pregnancy caused premature delivery (28.38). However, some studies showed no effect of anemia during pregnancy on premature delivery (27,39).

Newborn

Low birth weight infant

Several studies had been carried to demonstrate the correlation between hemoglobin level during pregnancy and low birth weight infant. Hemoglobin level less than 10.5 gm% during pregnancy had high correlation to small for gestational age newborn (36, 37, 40, 41, 42, 43). Newborn born to low serum ferritin pregnant mothers also had low birth weight (32,44). Study of teenage pregnancy showed that teenage pregnancy with anemia had higher incidence of low birth weight in infant than those with normal pregnancy (45,46). This finding was contrast to some studies which confirmed that anemia during pregnancy has no effect to birth weight (47).

Still birth

In a study from Papua Newguinea, high still birth rate was 94 cases to 1,000 birth in pregnancies having low level hemoglobin less than 6 gm/dL. Still birth rate in hemoglobin levels 10.0 – 10.9 gm/dL and more than 11 gm/dL were 14 and 18 cases per 1,000 birth, respectively (41). This finding was according to a study in teenage

pregnancy with anemia, which had high incidence of stillbirth (45). Hemoglobin level less than 6 mg% had high correlation with stillbirth (48).

Apgar score

The study conducted in India measured the effect of hemoglobin level and serum ferritin level on the outcome of pregnancy with anemia. It was demonstrated that an important cause of anemia in pregnancy was from iron deficiency anemia (RR = 0.40, $p < 0.001$) and hemoglobin level during pregnancy had high correlation to Apgar score ($p < 0.001$) (32).

Birth Asphyxia

The same study in India also demonstrated that hemoglobin level during pregnancy had high correlation to birth asphyxia as defined as Apgar score(32).

Head Circumference and Length of Newborn

The study involving the effect of anemia during pregnancy on intrauterine fetal growth showed that newborns delivered by moderate anemia mothers (Hemoglobin level 6.1+/- 8.5 g/dl), by severe anemia mothers (Hemoglobin level < or = 6.1 g/dl), and by low serum ferritin level during pregnancy (serum ferritin level < 10 micrograms/L) had head circumferences and lengths less than the newborns delivered by normal pregnancy mothers (44).

2. Effect of Thalassemias on pregnancy

Table 1 demonstrated etiologies of anemia during pregnancy. One of the

genetic cause is Thalassemias, a group of hereditary anemias, This disease arises from defects in the synthesis of globin chains. Abnormal synthesis rates may result in ineffective erytropoiesis, hemolysis, and varying degrees of anemia. The different forms of Thalassemia are classified according to the globin chain which is deficient in amount compared with its partner chain. The two major forms of Thalassemias involve either impaired production of alpha peptide chains causing α-Thalassemia, or of beta chains causing β-Thalassemia (8).

Thalassemias have a lot of impact to the body system mainly on abnormal in red blood cell production and result in low hemoglobin synthesis. These mutant hemoglobins can aggregate to form inclusion bodies that adhere to cell membranes, promote oxidative damage to the membrane, diminish cell deformability, and shorten red cell survival. The blood smear shows hypochromic microcytes and nucleated RBCs. Furthermore, efficacy of red blood cell to carry oxygen supply to tissue is less than 10 times of normal. Signs and symptoms of Thalassemias are anemia, hepatosplenomegaly, characteristic bone changes, growth retardation, delayed puberty, infertility, and prone to infections. Severe cases required blood transfusion for the treatment of severe anemia might have complications of long-term blood transfusion.

Studies of effects of Thalassemias on pregnancy.

Prognosis of Thalassemias disease

One of the reports from Israel demonstrated that a homozygous β-Thalassemias major patient who had severe anemia and splenectomy was performed at the age of 11 years needed regular blood transfusion to maintain hemoglobin level at

about 9 gm/dl. She had been on various regimens for induction of ovulation for many years and finally was pregnant. Her full term baby (birth weight 3,000 gm) was delivered by caesarian section (49). Other studies from Greece and Japan also reported successful term pregnancies in Thalassemia major and Thalassemia intermedia mother with no complications under carefully appropriate care by an experienced medical team (50,51).

Similar study from United Arab Emirates reported that successful outcome of pregnancies does occur in women with transfusion-dependent β-Thalassemias major and also in those with asymptomatic HIV disease (52,53).

Complications during pregnancy

A very interesting report from Hongkong demonstrated that pregnancy in thalasseimia trait had significantly high incidence of gestational glucose intolerance, but other complications were same as iron deficiency anemia (27).

Size and placental weight

Another report from Hongkong showed that both iron deficiency and Thalassemia trait pregnancy had high positive correlation to placental size and placental ratio ($p = 0.001$, $p < 0.001$ in iron deficiency anemia and $P = 0.011$, $p = 0.019$ in Thalassemia trait, respectively) (54).

Outcome of pregnancy

The study of screening blood mean corpuscular volume less than 80 fl at the first visit of prenatal care demonstrated that Thalassemia trait did not have any adverse effect on pregnancy outcome while the fetuses were at risk for Thalassemia disease. Thus it was concluded that the Thalassemia screening program is an effective and applicable means of detecting Thalassemia in antenatal care clinic (55).

Neonatal hyperbilirubinemia

The report about newborn born from alpha–Thalassemia minor mothers in Taipei showed that on day 3 after birth the incidence of hyperbilirubinemia (bilirubin level over 10 mg/dl) was significantly lower in new born of Thalassemia mother than new born in control group (0.9% vs 9.5%, Fisher's exact probability = 0.0012). The incidence of photo therapy was also significantly lower in new born of Thalassemia mother (20%) than in new born of control group (31%) (56).

3. Thalassemia status in Thailand

The study about Thalassemia status in Thailand by Vicharn Panich et al. showed that the incidence of α Thalassemia 1 was 0.02 in all parts of Thailand whereas α Thalassemia 2 varied among different regions. The lowest was in the southern part of Thailand (Songkhla, about 0.06), and the highest was in the north-eastern part of Thailand (Khonkean, about 0.17), especially in among people in Sakon Nakorn province called "So" (about 0.36).

The prevalence of β Thalassemia gene in all part of Thailand was average from 0.01 – 0.03, higher in the northern part and lower region of the north-eastern part. The highest prevalence of β Thalassemia was 0.05 in mountain people in the northern part of Thailand.

The prevalence of Hemoglobin E gene was contrast to β Thalassemia disease. The highest prevalence of hemoglobin E disease was in the north-eastern part of Thailand whereas lowest is in the northern part. An area of highest prevalence of hemoglobin E disease (about 74%) called 'triangle of hemoglobin E' was the connecting border of three countries (Cambodia, Laos, and Thailand) at lower region of north-eastern region of Thailand (57).

Molecular genetic study of Thalassemia in Thailand demonstrated more than a hundred types of abnormal gene. This caused various types of signs and symptoms of Thalassemia disease which range from asymptomatic except abnormal hemoglobin electrophoresis to severe form of Thalassemia disease.

Because of different prevalence of Thalassemia disease among regions in Thailand, many molecular genetic studies of pathogenesis and intrauterine diagnosis of Thalassemia disease were conducted for the purpose of reduction of incidence of Thalassemia disease and also to reduce economic loss (58,59,60,61).

CHAPTER III

MATERIALS AND METHODS

Study design

The study design is a retrospective cohort study to demonstrate the outcome of Thalassemia pregnancy.

Study population

Pregnant women who are resident of the upper northern region of Thailand.

Study subjects

The subjects were pregnant mothers who attended at the Mother and Child Hospital Chiang Mai, between 1st December 1997 to 15th June 1999.

Index groups were pregnant women with a confirmed diagnosis of Thalassemia. One tube osmotic fragility test (OF), dichlorophenol- indophenol (DCIP) and hemoglobin typing (4, 62) were screening tests for Thalassemia diagnosis.

Comparative groups were non-Thalassemia pregnant women who attended the antenatal clinic (ANC) matched to the Thalassemia pregnant women for the date of the first ANC visit.

Study size

This study was set to have 95% confidence level and 80% power of test. The sample size was calculated with 95% confidence level and 80% power of test for several variables which yielded different sample sizes as shown below:

Variable	Study size
Premature delivery	772
Hypertension in pregnancy	27
Post partum hemorrhage	474
Low birth weight infant	38

The required study size was 772, however due to limitation of time and available fund, it was necessary to limit study size to 464.

Data collection

Data were collected during the study period from 1st December 1997 to 15th June 1999. All relevant information were taken from the hospital records (ANC record, OPD card and admission charts). It contains 6 part as follows.

1. Demographic characteristics
2. Reproductive characteristics
3. Pregnancy progression
4. Pregnancy outcome
5. Birth outcome
6. Maternal and neonatal postpartum follow up

Data processing

Data were periodically checked, verified and cleaned to improve the quality. Complete data record of 464 samples were processed such as coding, editing using EPI info version 6.04 program from a microcomputer.

Data analysis

Data were analyzed by using STATA program version 5.0 from a microcomputer, and association was considered statistically significant if two tail p-value < 0.05.

The variables were categorized as either dependent of independent and either continuous, ordinal, or nominal and was analyzed by using appropriate statistical tests.

Statistical analysis

1. Descriptive statistics

Frequency and percentage were presented for demographic and other characteristics of the study subjects for categorical independent data. Mean and standard deviation were calculated for numerical independent data.

2. Analytical statistics. Following statistical methods were applied:

2.1 Univariate method

- Using exact probability test for categorical data if small table size.

- Using Chi - square test for categorical data if large table size.

- Using Kruskal – Wallis test for skewed distribution data.

- Generalized linear modeling was applied for analysis in order to show effect of significant association between Thalassemia and pregnancy outcome.

- Linear regression was applied for continuous data

- Exponential risk regression was applied for dichotomous data

2.2 Multivariate method

Potential confounders of each outcome measure were controlled by regression technique using generalized linear modeling.

- Exponential regression was used for dichotomous data

- Linear regression was used for continuous data

CHAPTER IV

RESULTS

The pregnancy outcome of Thalassemia was evaluated using a retrospective cohort study. The subjects were pregnant women who attended at the Mother and Child Hospital, Chiang Mai, between 1st December 1997 and 15th June 1999. There were 464 study subjects, comprised of 13 cases of Thalassemia disease pregnancy, 132 cases of Thalassemia trait pregnancy, and 319 cases of non- Thalassemia pregnancy.

Percentages of Thalassemia trait pregnancy as follow:

Alpha – Thalassemia trait	20.4 %	(27 cases)
Beta – Thalassemia trait	20.4 %	(27 cases)
Hb E trait	59.2 %	(78 cases)

Percentages of Thalassemia disease pregnancy as follow:

Homozygous Hb E	30.8 %	(4 cases)
Beta thal/Hb E	7.7 %	(1 case)
Hb H disease	61.5 %	(8 cases)

The results were presented in the following five areas:

1. Demographic characteristics
2. Pregnancy progression
3. Pregnancy outcome
4. Obstetric outcome

5. Maternal and neonatal postpartum follow up.

1. Demographic characteristics

1.1 General characteristics in this study are presened in table 4.

Age: The average age was 25.37 years (SD = 5.52) in non-Thalassemia pregnancies, 26.10 years (SD = 6.61) in Thalassemia trait pregnancies, and 26.15 years (SD = 5.83) Thalassemia disease pregnancies. The differences were not statistically significant (p = 0.690).

Race: Most of the subjects in this study were Thai. The percentage of Thai subjects in non-Thalassemia, Thalassemia trait, and Thalassemia disease pregnancies were 92.2%, 97.7% and 92.3%, respectively. Exact probability test was statistically significant (p = 0.046).

Marital status: Most of the participants were married, and they represented 99.4% in non-Thalassemia pregnancies, 97.7% in Thalassemia trait pregnancies, and 92.3% in Thalassemia disease pregnancies. Widowed/ separated accounted for 0.6% in non-Thalassemia pregnancies, 2.3% in Thalassemia trait pregnancies, and 7.7% in Thalassemia disease pregnancies. Exact probability test was statistically significant (p = 0.041).

Religion: The subjects of this study were mainly Buddhists: 96.6% in non-Thalassemia pregnancies, 98.4% in Thalassemia trait pregnancies, and 100.0% in

Thalassemia disease pregnancies. Exact probability test was not statistically significant (p = 0.343).

Occupation: According to the distribution of occupation, employees was the major group, and they represented 54.2% in non-Thalassemia pregnancies, 66.7% in Thalassemia trait pregnancies, and 69.2% in Thalassemia disease pregnancies. Housewife was the second major group, and they represented 26.7% in non-Thalassemia pregnancies, 19.7% in Thalassemia trait pregnancies, and 23.1% in Thalassemia disease pregnancies. The Chi-square test was not statistically significant (p = 0.260).

Education: The levels of education among these three groups were similar. Most of them had primary and secondary schooling: 78.4% in non-Thalassemia pregnancies, 82.2% in Thalassemia trait pregnancies, and 84.6% in Thalassemia disease pregnancies. The difference among the three groups was not statistically significant (p=959).

Height: The distribution of height among the three groups was not statistically significant (p=0.428). The mean height was 153.55 cm. (SD=5.87) in non-Thalassemia pregnancies, 153.01 cm. (SD=5.58) in Thalassemia trait pregnancies, and 151.82 cm. (SD=4.73) in Thalassemia disease pregnancies.

Pre-pregnancy weight: The average weight of pre-pregnancies was 50.32 kg. (SD=9.95) in non-Thalassemia pregnancies, 51.85 kg. (SD=11.22) in Thalassemia trait

pregnancies, and 44.33 kg. (SD = 3.06) in Thalassemia disease pregnancies. The differences were not statistically significant (p = 0.312).

Underlying disease of pregnant women: Most of the participants among the three groups had no underlying disease: 92.8% in non-Thalassemia pregnancies, 90.9% in Thalassemia trait pregnancies, and 100.0% in Thalassemia disease pregnancies. The differences were not statistically significant (p = 0.580).

Family history of illness: Most of the participants among all the three groups had no family history of illness: 83.4% in non-Thalassemia pregnancies, 81.1% in Thalassemia trait pregnancies, and 84.6% in Thalassemia disease pregnancies. The differences were not statistically significant (p = 0.878).

Table 4 General characteristics of subjects classified by thalassemia.

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Age (years)							
13 – 19	40	12.5	27	20.5	0	0.0	0.022
20 – 34	257	80.6	89	67.4	11	84.6	
35 – 45	21	6.6	14	10.6	2	15.4	
≥ 46	1	0.3	2	1.5	0	0.0	
Mean (SD)	25.37	(5.52)	26.10	(6.61)	26.15	(5.83)	0.690[a]
Range	14 - 46		14 - 47		20 - 39		
Race							
Thai	294	92.2	129	97.7	12	92.3	0.046
Other	25	7.8	3	2.3	1	7.7	
Marital Status							
Married	317	99.4	129	97.7	12	92.3	0.041
Widowed / separated	2	0.6	3	2.3	1	7.7	

* Exact probability test [a] Kruskal – Wallis test

Table 4 General characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Religion							
Buddhism	308	96.6	130	98.4	13	100.0	0.343
Christian	10	3.1	1	0.8	0	0.0	
Muslim	0	0.0	1	0.8	0	0.0	
Other	1	0.3	0	0.0	0	0.0	
Occupation							
House wife	85	26.7	26	19.7	3	23.1	0.260[a]
Government official	9	2.8	2	1.5	0	0.0	
Employee / Agriculture	173	54.2	88	66.7	9	69.2	
Business	51	16.0	14	10.6	1	7.7	
Other	1	0.3	2	1.5	0	0.0	

* Exact probability test [a] Chi square test

Table 4 General characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Education							
No education	24	7.7	7	5.4	1	7.7	0.959[a]
Primary	118	37.9	52	40.3	6	46.1	
Secondary	126	40.5	54	41.9	5	38.5	
Diploma / bachelor and higher level	43	13.9	16	12.4	1	7.7	
Height (cm.)							
131 – 145	27	8.6	13	9.9	1	9.1	0.901
146 – 160	256	81.3	104	79.4	10	90.9	
161 – 175	32	10.1	14	10.7	0	0.0	
Mean (SD)	153.55	(5.87)	153.01	(5.58)	151.82	(4.73)	0.428[b]
Range	135 - 170		138 - 166		145 - 160		

* Exact probability test [a] Chi square test [b] Kruskal – Wallis test

Table 4 General characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Prepregnancy weight (kg.)							
29 -45	24	35.3	11	35.5	2	66.7	0.606
46 – 60	38	55.9	14	45.2	1	33.3	
61 - 75	4	5.9	4	12.9	0	0.0	
≥76	2	2.9	2	6.4	0	0.0	
Mean (SD)	50.32	(9.95)	51.85	(11.22)	44.33	(3.06)	0.312[a]
Range	35 - 92		30 - 88		41 - 47		
Underlying disease of pregnant women							
No	285	92.8	120	90.9	13	100.0	0.580
Yes	22	7.2	12	9.1	0	0.0	
Renal calculus	0	0.0	2	1.5	0	0.0	0.143

* Exact probability test [a] Kruskal – Wallis test

Table 4 General characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Mass in nose	0	0.0	1	0.8	0	0.0	0.322
Molar pregnancy	0	0.0	1	0.8	0	0.0	0.322
Appendicitis	2	0.7	2	1.5	0	0.0	0.633
Asthma	6	1.9	1	0.8	0	0.0	0.738
Myoma uteri	1	0.3	0	0.0	0	0.0	1.000
Hypertension	1	0.3	1	0.8	0	0.0	0.540
Malaria	1	0.3	1	0.8	0	0.0	0.540
Thyroid	4	1.3	2	1.5	0	0.0	1.000
Pulmonary TB	2	0.7	0	0.0	0	0.0	1.000
Fragure spine	0	0.0	1	0.8	0	0.0	0.322
Fragure Pelvis	2	0.7	0	0.0	0	0.0	1.000
Pyelonephritis	1	0.3	0	0.0	0	0.0	1.000
Diabetes mellitus	2	0.7	0	0.0	0	0.0	1.000

* Exact probability test

Table 4 General characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Family history of illness							
No	257	83.4	107	81.1	11	84.6	0.878
Yes	51	16.6	25	18.9	2	15.4	
Diabetes mellitus and Hypertension	4	1.3	1	0.8	0	0.0	1.000
Hypertension	17	5.5	4	3.0	0	0.0	0.568
Diabetes mellitus	16	5.2	12	9.1	2	15.4	0.143
Asthma	9	2.9	7	5.3	0	0.0	0.539
Congenital anomaly	1	0.3	1	0.8	0	0.0	0.539
Heart disease	2	0.7	0	0.0	0	0.0	0.633
Epilepsy	1	0.3	0	0.0	0	0.0	1.000
Thyroid	1	0.3	0	0.0	0	0.0	1.000

* Exact probability test

1.2 The reproductive characteristics in this study are presented in table 5.

Gravida: Most of the participants these three groups were nullipara: 43.7% in non-Thalassemia pregnancies, 44.7% in Thalassemia trait pregnancies, and 61.5% in Thalassemia disease pregnancies. The next most common was 2nd gravida: 43.1% in non-Thalassemia pregnancies, 37.9% in Thalassemia trait pregnancies, and 30.8% in Thalassemia disease pregnancies. 3rd, 4th and 5th gravida were similar among these three groups of pregnancies. Interestingly, 0.3% pregnancy in Thalassemia disease group had 6th gravida which was significantly higher than the other groups (p=0.003).

Parity: Most of the participants these three groups had no parity. The percentage of no parity in non-Thalassemia, Thalassemia trait, and Thalassemia disease pregnancies were 54.4%, 56.8%, and 76.9%, respectively. The differences were not statistically significant (p=0.525).

History of Abortion: The history of abortion among the participants of non-Thalassemia, Thalassemia trait, and Thalassemia disease pregnancies were 18.9%, 25.8%, and 23.1%, respectively. The differences were statistically significant (p=0.010).

Living Children: The percentage of no living children in non-Thalassemia, Thalassemia trait, and Thalassemia disease pregnancies were 55.0%, 58.3%, and 76.9%, respectively.

Previous premature delivery: Most of the participants in all three groups had no previous premature delivery: 96.4% in non-Thalassemia pregnancies, 93.9% in Thalassemia trait pregnancies, and 100.0% in Thalassemia disease pregnancies. Exact probability test was not statistically significant (p=0.416).

Previous low birth weight infant: Most of the participants these three groups had no previous low birth weight infant: 95.2% in non-Thalassemia pregnancies, 93.9% in Thalassemia trait pregnancies, and 100.0% in Thalassemia disease pregnancies. Exact probability test was not statistically significant (p=0.819).

Table 5 Reproductive characteristics of subjects classified by thalassemia.

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Gravida							
Nullipara	139	43.7	59	44.7	8	61.5	0.003
2	137	43.1	50	37.9	4	30.8	
3	34	10.7	19	14.4	0	0.0	
4	7	2.2	2	1.5	0	0.0	
5	0	0.0	2	1.5	0	0.0	
6	1	0.3	0	0.0	1	7.7	
Parity							
No	173	54.4	75	56.8	10	76.9	0.525
1	129	40.6	49	37.1	2	15.4	
2	15	4.7	6	4.6	1	7.7	
3	0	0.0	1	0.8	0	0.0	
4	0	0.0	1	0.8	0	0.0	
5	1	0.3	0	0.0	0	0.0	

* Chi square test

Table 5 Reproductive characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
History of abortion							
No	258	81.1	98	74.2	10	76.9	0.010
1	53	16.7	34	25.8	2	15.4	
2	7	2.2	0	0.0	0	0.0	
3	0	0.0	0	0.0	1	7.7	
Number of living children							
No	175	55.0	77	58.3	10	76.9	0.528[a]
1	126	39.6	47	35.6	2	15.4	
2	16	5.0	6	4.5	1	7.7	
3	0	0.0	1	0.8	0	0.0	
4	0	0.0	1	0.8	0	0.0	
5	1	0.4	0	0.0	0	0.0	

* Exact probability test [a] Chi square test

Table 5 Reproductive characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Number of previous premature delivery							
No	298	96.4	124	93.9	13	100.0	0.416
1	11	3.6	8	6.1	0	0.0	
Number of previous low birth weight delivery							
No	294	95.2	124	93.9	13	100.0	0.819
1	15	4.8	8	6.1	0	0.0	

* Exact probability test

2. Pregnancy progressions in this study are presened in table 6.

Attending antenatal care: Most of the subjects of this study had attended antenatal care clinic 4 times. The percentage of 4 ANC visits at the antenatal care clinic among the non-Thalassemia, Thalassemia trait, and Thalassemia disease pregnancies were 56.4%, 63.0%, and 41.7%, respectively. Exact probability test was not statistically significant (p=0.251).

Screening serology test for HIV infection: Most of the subjects were HIV negative: 96.2% in non-Thalassemia pregnancies, 98.0% in Thalassemia trait pregnancies, and 100.0% in Thalassemia disease pregnancies. Exact probability test was not statistically significant (p=0.623).

Screening serology test for syphilis: Most of the study subjects were negative: 97.8% in non-Thalassemia pregnancies, 98.5% in Thalassemia trait pregnancies, and 100.0% in Thalassemia disease pregnancies. Exact probability test was not statistically significant (p=1.000).

Screening serology test for hepatitis B virus: The study subjects were mainly negative for hepatitis B surface antigen: 92.9% in non-Thalassemia pregnancies, 90.1% in Thalassemia trait pregnancies, and 100.0% in Thalas/ semia disease pregnancies. Exact probability test was not statistically significant (p=0.477).

Maternal weight at 1st visit: The average weight was 54.63 kg. (SD=10.02) in non-Thalassemia pregnancies, 53.35 kg. (SD=9.21) in Thalassemia trait pregnancies, and

54.62 kg. (SD = 7.57) in Thalassemia disease pregnancies. The differences were not statistically significant (p = 0.451).

Maternal weight gain: The average weight gain per week of the non-Thalassemia pregnancies was 0.40 kg. (SD=0.15). This was more than those of Thalassemia trait pregnancies (0.37 kg, SD=0.12) and those of Thalassemia disease pregnancies (0.31, SD=0.11). But the differences were not statistically significant (p = 0.429).

Body mass index (BMI): The mean BMI was 22.95 kg/m^2 (SD=3.76) in non-Thalassemia pregnancies, 22.54 kg/m^2 (SD=3.78) in Thalassemia trait pregnancies, and 22.86 kg/m^2 (SD=3.24) in Thalassemia disease pregnancies.The comparison of means BMI among these three groups were not statistically significant different (p=0.587).

Complication during pregnancy: 95.0% in non-Thalassemia pregnancies, 91.7% in Thalassemia trait pregnancies, and 100.0% in Thalassemia disease pregnancies had no complication during pregnancies. The comparison of complications during pregnancies among all three groups was not statistically significant different (p=0.530).

Hematocrit (Hct) at 1st visit: The mean Hct at the 1st visit was 37.75 % (SD=3.07) in non-Thalassemia pregnancies, 36.06 %(SD=3.05) in Thalassemia trait pregnancies, and 34.3 % (SD=2.58) in Thalassemia disease pregnancies. The comparison of means Hct among these three groups was statistically significant different (p<0.001).

Hematocrit (Hct) at 3rd trimester: The mean Hct at 3rd trimester was 37.69 % (SD=3.06) in non-Thalassemia pregnancies, 35.77 %(SD=3.27) in Thalassemia trait pregnancies, and 35.70 % (SD=2.06) in Thalassemia disease pregnancies. The comparison of means Hct among these three groups was statistically significant different ($p<0.001$).

Table 6 Pregnancy progression of subjects classified by thalassemia.

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Attending antenatal care							
No	134	43.6	47	37.0	7	58.3	0.251
Yes	173	56.4	80	63.0	5	41.7	
Number of antenatal care visit							
No	8	2.6	0	0.0	0	0.0	0.164[a]
1	39	12.7	15	11.8	4	33.3	
2	39	12.7	12	9.4	0	0.0	
3	48	15.6	20	15.8	3	25.0	
4	173	56.4	80	63.0	5	41.7	

* Exact probability test [a] Chi square test

Table 6 Pregnancy progression of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Screening serology test for HIV infection							
Negative	204	96.2	97	98.0	8	100.0	0.623
Positive	8	3.8	2	2.0	0	0.0	
Screening serology test for syphilis							
Negative	312	97.8	130	98.5	13	100.0	1.000
Positive	7	2.2	2	1.5	0	0.0	
Screening serology test for Hepatitis B virus							
Negative	289	92.9	118	90.1	13	100.0	0.477
Positive	22	7.1	13	9.9	0	0.0	

* Exact probability test

Table 6 Pregnancy progression of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Maternal weight at 1st visit (kg.)							
31 – 45	47	14.7	20	15.1	2	15.4	0.322[a]
46 – 60	189	59.3	90	68.2	7	53.8	
61 – 75	72	22.6	17	12.9	4	30.8	
≥ 76	11	3.4	5	3.8	0	0.0	
Mean (SD)	54.63	(10.02)	53.35	(9.21)	54.62	(7.57)	0.45[b]
Range	33.50 - 93.00		36.30 - 85.50		42.10 - 64.80		
Maternal weight gain (kg./wk.)							
0.01 – 0.49	50	73.5	25	80.7	3	100.0	0.595
0.50 – 0.99	18	26.5	6	19.3	0	0.0	
Mean (SD)	0.40	(0.15)	0.37	(0.12)	0.31	(0.11)	0.429[b]
Range	0.11 - 0.86		0.08 – 0.57		0.24 - 0.43		

* Exact probability test [a] Chi square test [b] Kruskal – Wallis test

Table 6 Pregnancy progression of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Body mass index (kg./m.^{2})							
<18.5	29	9.2	14	10.7	1	9.0	0.469[a]
18.5 – 24.9	198	62.9	87	66.4	5	45.5	
25.0 – 29.9	72	22.9	23	17.6	5	45.5	
≥ 30	16	5.0	7	5.3	0	0.0	
Mean (SD)	22.95	(4.03)	22.54	(3.78)	22.86	(3.24)	0.587[b]
Range	15.30 - 39.70		12.82 – 35.25		17.07 - 27.20		
Complication during pregnancy							
No	303	95.0	121	91.7	13	100.0	0.530
Hypertension during pregnancy							
	11	3.4	6	4.5	0	0.0	
PIH	4	1.3	5	3.8	0	0.0	
Chronic hypertension	1	0.3	0	0.0	0	0.0	

* Exact probability test [a] Chi square test [b] Kruskal - Wallis test

Table 6 Pregnancy progression of subjects classified by thalassemia (continued).

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Hematocrit at 1st visit (%)							
< 33	6	2.3	11	9.1	2	20.0	0.002
≥ 33	257	97.7	110	90.9	8	80.0	
Mean (SD)	37.75	(3.07)	36.06	(3.05)	34.3	(2.58)	<0.001[a]
Range	31 - 47		24 - 43		30 - 38		
Hematocrit at 3rd trimester(%)							
< 33	9	4.6	9	12.2	0	0.0	0.090
≥ 33	187	95.4	65	87.8	10	100.0	
Mean (SD)	37.69	(3.06)	35.77	(3.27)	35.70	(2.06)	<0.001[a]
Range	30 - 48		22 - 43		33 - 39		
Difference of hematocrit level during pregnancy (%)							
Mean (SE)	0.22	(0.26)	0.13	(0.37)	-1.14	(1.40)	
p-value	0.414		0.727		0.447		

* Exact probability test [a] Kruskal – Wallis test

3. Pregnancy outcome

3.1 Pregnancy outcomes in this study are presented in table 7.

Gestation age: The distribution of gestational age among three groups was similar. The mean gestational age was 38.66 weeks (SD=1.92) in non-Thalassemia pregnancies, 38.62 weeks (SD=1.81) in Thalassemia trait pregnancies, and 38.69 weeks (SD=1.38) in Thalassemia disease pregnancies. The means of gestational age among these groups were not statistically significant different (p=0.975)

Pregnancy outcome: Most of the subjects had term delivery. The percentage of term delivery in non-Thalassemia, Thalassemia trait, and Thalassemia disease pregnancies were 89.0 %, 87.9%, and 100.0%, respectively. The differences among these groups were not statistically significant different (p=0.843).

Neonatal status at delivery: All the subjects had live birth.

Table 7 Pregnancy outcome of subjects classified by thalassemia.

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Gestational age (week)							
Mean (SD)	38.66	(1.92)	38.62	(1.81)	38.69	(1.38)	0.975 [a]
Range	30 – 46		32 - 43		37 - 41		
Pregnancy outcome							
Term	284	89.0	116	87.9	13	100.0	0.843
Premature	30	9.4	14	10.6	0	0.0	
Postterm	5	1.6	2	1.5	0	0.0	
Neonatal status at delivery							
Livebirth	319	100.0	132	100.0	13	100.0	
Stillbirth	0	0.0	0	0.0	0	0.0	

* Exact probability test [a] Kruskal – Wallis test

3.2 Multivariate analysis of outcomes of pregnancy in Thalassemia and non-Thalassemia pregnancies is shown in table 8.

Maternal weight gain: After adjusting for age, gravida, HIV infection, complication during pregnancies, number of antenatal care visit and body mass index, maternal weight gain of Thalassemia trait and Thalassemia disease pregnancies were less than non-Thalassemia pregnancies, the mean differences were -0.02 kg/week (95%CI = -0.07 to 0.02, p=0.309) and -0.02 kg/week (95%CI= -0.16 to 0.13, p=0.837), respectively.

Hematocrit at 1st ANC visit: After adjusting for maternal weight gain, Hct at 1st ANC visit of Thalassemia trait and Thalassemia disease pregnancies were lower than non-Thalassemia pregnancies. The significant differences were -1.69% (95%CI= -2.35 to -1.03, p<0.001) and -3.45% (95%CI= -5.39 to –1.52, p<0.001), respectively.

Hematocrit at 3rd trimester: After adjusting for maternal weight gain, the Hct levels at 3rd trimester of Thalassemia trait and Thalassemia disease pregnancies were lower than non-Thalassemia pregnancies. The significant differences were –1.92% (95%CI= -2.75 to -1.09, p<0.001) and –1.99% (95%CI= -3.96 to –0.02, p=0.047).

Complication during pregnancy. After adjusting for age and gravida, the Thalassemia trait and the Thalassemia disease pregnancies had increased risk of complication during pregnancy (RR=1.66, 95%CI= 0.79 to 3.48, p=0.193 and RR=1.53, 95%CI= 0.22 to 10.70, p=0.688).

Table 8 Multivariate analysis for pregnancy progression, mean difference or risk ratio, 95% limit and p-value.

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Maternal weight gain (kg/wk.) [@a]								
	-0.02	-0.07	0.02	0.309	-0.02	-0.16	0.13	0.837
Hct at 1st visit (%) [@b]	-1.69	-2.35	-1.03	<0.001	-3.45	-5.39	-1.52	<0.001
Hct at 3rd trimester (%) [@b]	-1.92	-2.75	-1.09	<0.001	-1.99	-3.96	-0.02	0.047
Complication during pregnancy [c]								
	[#]1.66	0.79	3.48	0.193	[&]1.53	0.22	10.70	0.688

[@] mean difference
[#] risk ratio
[&] estimate risk ratio
[a] adjusted for age, gravida, HIV infection, complication during pregnancy, number of antenatal care visit, body mass index
[b] adjusted for maternal weight gain
[c] adjusted for age, gravida

3.3 Multivariate analysis of outcomes of pregnancy in Thalassemia. and non-Thalassemia pregnancies is shown in table 9.

Gestational age: After adjusting for age, gravida, complication during pregnancy, underlying disease of pregnant women, and the number of previous premature delivery, the average gestational age of Thalassemia trait pregnancies was shorter than non-Thalassemia pregnancies, and the mean difference was –0.04 week (95%CI= -0.43 to 0.34, p=0.822). Whereas, Thalassemia disease pregnancies were longer than non-Thalassemia pregnancies, and the mean difference was 0.04 week (95%CI= -1.02 to 1.09, p=0.948).

Premature delivery: After adjusting for history of abortion, number of previous premature delivery, and HIV infection, Thalassemia trait pregnancies had higher risk of premature delivery (RR=1.13, 95%CI= 0.62 to 2.06, p=0.728). Whereas, Thalassemia disease pregnancies had lower risk of premature delivery (RR=0.82, 95%CI= 0.12 to 5.54, p=0.835).

Table 9 Multivariate analysis for pregnancy outcome, mean difference or risk ratio, 95% limit and p-value.

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Gestational age (week) [@a]	-0.04	-0.43	0.34	0.822	0.04	-1.02	1.09	0.948
Premature delivery [b]	[#]1.13	0.62	2.06	0.728	[&]0.82	0.12	5.54	0.835

[@] mean difference
[#] risk ratio
[&] estimate risk ratio
[a] adjusted for age, gravida, complication during pregnancy, underlying disease of pregnant women, number of previous premature delivery
[b] adjusted for history of abortion, number of previous premature delivery, HIV infection

4. Obstetric outcomes

4.1 Obstetric outcomes are shown in table 10.

Rupture membrane before delivery: The duration of rupture membrane before delivery among these three groups was similar. The means was 273.35 minutes (SD=358.95) in non-Thalassemia pregnancies. 289.47 minutes (SD=349.26) in Thalassemia trait pregnancies, and 203.75 minutes (SD=241.29) in Thalassemia disease pregnancies. The comparison of these means was not statistically significant different (p=0.597). Most of the subjects had rupture membrane 24 hours before delivery. The percentage of rupture membrane 24 hours before delivery in non-Thalassemia, in Thalassemia trait, and in Thalassemia disease pregnancies were 95.7%, 93.3%, and 100%, respectively.

Type of membranes rupture: Most of the participating subjects in this study had artificial membranes rupture. The percentage of artificial membranes rupture in non-Thalassemia, Thalassemia trait, and Thalassemia disease pregnancies were 62.9%, 56.3%, and 66.7%, respectively. The difference among these groups was not statistically significant (p=0.644).

Amniotic fluid: Most of the subjects had clear amniotic fluid: 80.1% in non-Thalassemia pregnancies, 69.7% in Thalassemia trait pregnancies, and 71.4% in Thalassemia disease pregnancies. The difference among these groups was not statistically significant (p=0.415).

Mode of delivery: Most of subjects had normal delivery: 66.8% in non-Thalassemia pregnancies, 69.7% in Thalassemia trait pregnancies, and 92.3% in Thalassemia disease pregnancies. The difference among these groups was not statistically significant (p=0.575).

Indication for abnormal delivery: 34.5% in non-Thalassemia pregnancies, 33.3% in Thalassemia trait pregnancies, and 7.7% in Thalassemia disease pregnancies had indication for abnormal delivery. The difference among these groups was not statistically significant (p=0.347).

Duration of labour

First stage labour: The average duration of first stage labour of non-Thalassemia pregnancies was 369.65 minutes (SD=173.12) which was less than those of the Thalassemia trait pregnancies (401.47 minutes, SD=153.92) and those of Thalassemia disease pregnancies (430.00 minutes, SD=109.96). The differences were not statistically significant (p = 0.493).

Second stage labour in nullipara: The average duration of second stage labour of non-Thalassemia pregnancies was 27.54 minutes (SD=23.87). It was more than those of the Thalassemia trait pregnancies (26.22 minutes, SD=20.23) and those of Thalassemia disease pregnancies (25.13 minutes, SD=20.57). The differences were not statistically significant (p = 0.972). Most of the subjects had no prolonged labour: 87.7% in non-Thalassemia pregnancies, 93.9% in Thalassemia trait pregnancies, and 87.5% in Thalassemia disease pregnancies.

Second stage labour in multipara: The average duration second stage of labour was 20.22 minutes (SD=14.78) in non-Thalassemia pregnancies, 22.27 minutes (SD=17.71) in Thalassemia trait pregnancies. and 18.60 minutes (SD=12.23) in Thalassemia disease pregnancies. The differences among these groups were not statistically significant (p = 0.948). Most of the subjects had no prolonged second stage of labour: 84.6% in non-Thalassemia pregnancies, 73.3% in Thalassemia trait pregnancies, and 80.0% in Thalassemia disease pregnancies.

Third stage labour: The average duration of third stage labour of non-Thalassemia pregnancies was 6.74 minutes (SD=6.85), Thalassemia trait pregnancies was 6.06 minutes (SD=4.56), and Thalassemia disease pregnancies was 6.92 minutes (SD=4.75). The differences were not statistically significant (p = 0.688). Most of the subjects had no prolonged labour: 97.7% in non-Thalassemia pregnancies, 100.0% in Thalassemia trait pregnacies, and 100.0% in Thalassemia disease pregnancies.

Total duration of labour: The average of total duration of labour in non-Thalassemia pregnancies was 426.86 minutes (SD=176.67). This was less than those of Thalassemia trait pregnancies (431.58 minutes, SD=155.33) and those of Thalassemia disease pregnancies (459.54 minutes, SD=116.52). The differences were not statistically significant (p = 0.565).

Blood loss: The average blood loss was 361.16 cc. in non-Thalassemia pregnancies (SD=105.19), 360.39 cc.in Thalassemia trait pregnancies (SD=116.09), and 338.46 cc.

in Thalassemia disease pregnancies (SD=138.68). The differences were not statistically significant (p = 0.363).

Postpartum hemorrhage: Most of the subjects had no postpartum hemorrhage: 97.2% in non-Thalassemia pregnancies, 96.2% in Thalassemia trait pregnancies, and 92.3% in Thalassemia disease pregnancies. The differences were not statistically significant (p = 0.322).

Placenta weight: The average placenta weight was 586.43 gm. (SD=100.03) in non-Thalassemia pregnancies, 589.06 gm. (SD=105.72) in Thalassemia trait pregnancies, and 584.62 gm. (SD=89.13) in Thalassemia disease pregnancies. The differences were not statistically significant (p = 0.948).

Cord length: Cord lengths among three groups were not statistically significant (p=0.185). The mean cord length was 51.31 cm. (SD=9.33) in non-Thalassemia pregnancies, 51.68 cm. (SD=10.50) in Thalassemia trait pregnancies, and 59.00 cm. (SD=15.58) in Thalassemia disease pregnancies.

Placenta characteristics: Most of the subjects had normal placenta characteristics. The percentage of normal placenta characteristics in non-Thalassemia, in Thalassemia trait, and in Thalassemia disease pregnancies were 97.5%, 97.6%, and 92.3%, respectively. The differences were not statistically significant (p = 0.298).

Table 10 Obstetric outcome of subjects classified by thalassemia.

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Rupture membranes before delivery							
Before 24 hours	45	95.7	14	93.3	1	100.0	1.000
After 24 hours	2	4.3	1	6.7	0	0.0	
Mean (SD)	273.35	(358.95)	289.47	(349.26)	203.75	(241.29)	0.597 [a]
Range	1 - 2160		3 - 1790		16 - 829		
Type of membranes rupture							
Spontaneous rupture of membranes	61	25.7	33	32.0	3	33.3	0.644
Spontaneous leak of membranes	27	11.4	12	11.7	0	0.0	
Artificial rupture of membranes	149	62.9	58	56.3	6	66.7	

* Exact probability test [a] Kruskal – Wallis test

Table 10 Obstetric outcome of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Amniotic fluid							
Clear	157	80.1	53	69.7	5	71.4	0.415
Mild	21	10.7	12	15.8	1	14.3	
Moderate	2	1.0	1	1.3	0	0.0	
Thick	16	8.2	10	13.2	1	14.3	
Mode of delivery							
Normal	213	66.8	92	69.7	12	92.3	0.575 [a]
Forceps extraction	21	6.6	8	6.1	0	0.0	
Vacuum extraction	24	7.5	9	6.8	1	7.7	
Cesarean section	61	19.1	23	17.4	0	0.0	

* Exact probability test [a] Chi square test

Table 10 Obstetric outcome of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Indication for abnormal delivery							
Normal	209	65.5	88	66.7	12	92.3	0.347
Indication by mother	76	23.8	36	27.3	1	7.7	
Indication by neonatal	29	9.1	8	6.0	0	0.0	
prophylaxis	5	1.6	0	0.0	0	0.0	
Duration of labour							
First stage labour (min.)							
Mean (SD)	369.65	(173.12)	401.47	(153.92)	430.00	(109.96)	0.493 [a]
Range	60 - 1480		75 - 850		285 - 720		

* Exact probability test [a] Kruskal – Wallis test

Table 10 Obstetric outcome of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Second stage labour (min.)							
Nullipara							
Mean (SD)	27.54	(23.87)	26.22	(20.23)	25.13	(20.57)	0.972 [a]
Range	2 - 164		3 - 95		3 - 68		
Prolonged labour							
No	100	87.7	46	93.9	7	87.5	0.423
Yes	14	12.3	3	6.1	1	12.6	
Multipara							
Mean (SD)	20.22	(14.78)	22.27	(17.71)	18.60	(12.23)	0.948 [a]
Range	2 - 84		1 - 88		4 - 37		
Prolonged labour							
No	121	84.6	44	73.3	4	80.0	0.126
Yes	22	15.4	16	26.7	1	20.0	

* Exact probability test [a] Kruskal – Wallis test

Table 10 Obstetric outcome of subjects classified by thalassemia (continued).

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Third stage labour (min.)							
Mean (SD)	6.74	(6.85)	6.06	(4.56)	6.92	(4.75)	0.688[a]
Range	1 - 53		1 - 24		3 - 19		
Prolonged labour							
No	251	97.7	109	100.0	13	100.0	0.340
Yes	6	2.3	0	0.0	0	0.0	
Total duration of labour (min.)							
Mean (SD)	426.86	(176.67)	431.58	(155.33)	459.54	(116.52)	0.565[a]
Range	86 - 1550		113 - 873		292 - 742		

* Exact probability test [a] Kruskal – Wallis test

Table 10 Obstetric outcome of subjects classified by thalassemia (continued).

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Blood loss (cc.)							
0 – 250	10	3.2	6	4.6	0	0.0	0.359
251 – 500	299	94.0	119	91.5	12	92.3	
501 – 750	7	2.2	4	3.1	0	0.0	
751 – 1,000	2	0.6	1	0.8	1	7.7	
Mean (SD)	361.16	(105.19)	360.39	(116.09)	338.46	(138.68)	0.363[a]
Range	100 - 1,000		200 - 1,000		300 - 800		
Postpartum hemorrhage							
No	309	97.2	125	96.2	12	92.3	0.322
Yes	9	2.8	5	3.8	1	7.7	

* Exact probability test [a] Kruskal – Wallis test

Table 10 Obstetric outcome of subjects classified by thalassemia (continued).

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Placenta weight (gm.)							
0 – 250	1	0.3	0	0.0	0	0.0	0.939
251 – 500	96	30.6	36	28.4	4	30.8	
501 – 750	200	63.7	83	65.3	8	61.5	
751 – 1,000	17	5.4	8	6.3	1	7.7	
Mean (SD)	586.43	(100.03)	589.06	(105.72)	584.62	(89.13)	0.948[a]
Range	200 - 1,000		320 - 1,000		500 - 800		
Cord length (cm.)							
0 – 25	0	0.0	1	0.8	0	0.0	0.031
26 – 50	188	59.9	78	61.4	5	38.5	
51 – 75	121	38.5	43	33.9	6	46.1	
76 – 100	5	1.6	5	3.9	2	15.4	
Mean (SD)	51.31	(9.33)	51.68	(10.50)	59.00	(15.58)	0.185[a]
Range	28 - 99		25 - 90		40 - 99		

* Exact probability test [a] Kruskal – Wallis test

Table 10 Obstetric outcome of subjects classified by thalassemia (continued).

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Placenta characteristic							
Normal	311	97.5	129	97.6	12	92.3	0.429
Abnormal	8	2.5	3	2.4	1	7.7	
Incomplete	0	0.0	1	0.8	0	0.0	0.298
Succenturiata	4	1.3	1	0.8	1	7.7	
Infarction	3	0.9	1	0.8	0	0.0	
Macerated placenta	1	0.3	0	0.0	0	0.0	

* Exact probability test

4.2 Neonatal outcomes are presented in table 11.

Gender: The gender of babies born to mothers in these three groups was similar. Male to female was 50: 50. The difference was not statistically significant (p = 0.559).

Birth weight: The average birth weight of the babies born to mothers was 3,119.56 gm. (SD=397.51) in non-Thalassemia mothers, 3,103.78 gm. (SD=400.79) in Thalassemia trait mothers, and 2,755.38 gm. (SD=331.57) in Thalassemia disease mothers. The differences were statistically significant (p=0.006). When subgroup analysis was carried out for only the term newborns, the result showed that babies born to Thalassemia disease mothers had significant low birth weight compared to the other groups (p = 0.042).

Birth length: The birth lengths of the babies were different: 51.60 cm. (SD=2.32) in non-Thalassemia mothers, 51.25 cm. (SD=3.07) in Thalassemia trait mothers, and 49.75 cm. (SD=2.67) in Thalassemia disease mothers. The difference were not statistically significant (p=0.113). When subgroup analysis only for the term newborns was done, again the birth length of the babies born to mother in Thalassemia disease group was significant shorter than the others (p = 0.020).

Head circumference: The average of baby's head circumferences was 32.92 cm. (SD=1.50) in non-Thalassemia mothers, 33.11 cm. (SD=1.44) in Thalassemia trait mothers, and 31.88 cm. (SD=1.40) in Thalassemia disease mothers. The differences were statistically significant (p=0.021).

Apgar score at 1 minute: Most of the babies had an 8-10 Apgar score at 1 minute: 91.8% in non-Thalassemia mothers, 96.2% in Thalassemia trait mothers, and 84.6% in Thalassemia disease mothers. The differences were not statistically significant ($p = 0.219$).

Apgar score at 5 minutes: Most of the babies had an 8-10 Apgar score at 5 minute: 95.3% in non-Thalassemia mothers, 100.0% in Thalassemia trait mothers, and 92.3% in Thalassemia disease mothers. The differences were statistically significant ($p = 0.010$).

Cord coiling: Most of the babies born to non-Thalassemia and Thalassemia trait mothers had no cord coiling 86.8% and 87.1%, respectively, but only 46.2% of the babies born to Thalassemia disease mothers had no cord coiling . This differences were statistically significant ($p = 0.005$).

Congenital anomaly: Most the of babies born to mothers had no congenital anomaly: 99.7% in non-Thalassemia mothers, 98.5% in Thalassemia trait mothers, and 92.3% in Thalassemia disease mothers. Babies in Thalassemia disease mothers had 7.7% cleft palate. There were statistically significant differences in terms of cleft palate of congenital anomaly among these groups ($p = 0.030$).

Birth complication: The babies had birth complication including meconium aspiration, body temperature>38°c, birth asphyxia and anemia: 23.5% in non-

Thalassemia mothers, 25.8% in Thalassemia trait mothers, and 46.2% in Thalassemia disease mothers. The differences were not statistically significant (p=0.178).

Table 11 Neonatal outcome of subjects classified by thalassemia.

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Gender							
Male	162	50.8	65	49.3	6	46.2	0.559
Female	157	49.2	66	50.0	7	53.8	
2 gender	0	0.0	1	0.7	0	0.0	
Birth weight (gm.)							
1,000 – 2,499	17	5.3	9	6.8	4	30.8	0.042
2,500 – 4,000	297	93.1	121	91.7	9	69.2	
4,001 – 4,500	5	1.6	2	1.5	0	0.0	
Mean (SD)	3,119.56	(397.51)	3,103.78	(400.79)	2,755.38	(331.57)	0.006[a]
Range	2,040 - 4,400		2,070 - 4,150		2,300 - 3,310		

* Exact probability test [a] Kruskal – Wallis test

Table 11 Neonatal outcome of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Birth length (cm.)							
31 – 40	0	0.0	1	0.8	0	0.0	0.020
41 – 50	91	28.8	50	37.9	7	58.3	
51 – 60	225	71.2	81	61.3	5	41.7	0.113[a]
Mean (SD)	51.60	(2.32)	51.25	(3.07)	49.75	(2.67)	
Range	46.0 - 60.5		33.0 - 57.0		45.0 - 53.0		
Head circumference (cm.)							
26 – 30	16	5.1	4	3.0	1	8.3	0.680
31 – 35	286	90.5	121	91.7	11	91.7	
36 – 40	14	4.4	7	5.3	0	0.0	
Mean (SD)	32.92	(1.50)	33.11	(1.44)	31.88	(1.40)	0.021[a]
Range	29.0 - 37.0		29.0 - 37.0		29.5 - 35.0		

* Exact probability test [a] Kruskal – Wallis test

Table 11 Neonatal outcome of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Apgar score at 1 minute							
8 – 10	290	91.8	127	96.2	11	84.6	0.219
4 – 7	23	7.3	5	3.8	2	15.4	
0 – 3	3	0.9	0	0.0	0	0.0	
Apgar score at 5 minute							
8 – 10	301	95.3	132	100.0	12	92.3	0.010
4 – 7	15	4.7	0	0.0	1	7.7	
Cord coiling							
No	277	86.8	115	87.1	6	46.2	0.005
1	34	10.7	13	9.9	6	46.2	
>1	8	2.5	4	3.0	1	7.6	

* Exact probability test

Table 11 Neonatal outcome of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Congenital anomaly							
No	318	99.7	130	98.5	12	92.3	0.032
Any anomaly	1	0.3	2	1.5	1	7.7	
No cavity right ear	0	0.0	1	0.8	0	0.0	0.314
Cleft palate	0	0.0	0	0.0	1	7.7	0.030
Lowset ear	0	0.0	1	0.8	0	0.0	0.314
Flat foot	1	0.3	0	0.0	0	0.0	1.000
Birth complication							
No	244	76.5	98	74.2	7	53.8	0.178
Any complication	75	23.5	34	25.8	6	46.2	
Meconium aspiration	35	11.0	19	14.4	4	30.8	0.146
Body temperature > 38° c	13	4.1	4	3.0	0	0.0	0.868
Anemia	1	0.3	6	4.6	0	0.0	0.010
Birth asphyxia	26	8.2	5	3.8	2	15.4	0.140

* Exact probability test

4.3 Multivariate analysis of outcomes of obstetric in Thalassemia and non-Thalassemia pregnancies is shown in table 12.

Membranes rupture before delivery: After adjusting for gestational age and occupation, Thalassemia trait and Thalassemia disease pregnancies showed low risk of membranes rupture before delivery (RR=0.74, 95%CI= 0.44 to 1.27, p=0.281 and RR=0.45, 95%CI= 0.07 to 2.97, p=0.404).

Duration membranes rupture: After adjusting for gestational age, the Thalassemia trait pregnancies had longer duration of membranes rupture than non-Thalassemia pregnancies. The mean difference was 16.13 minutes (95%CI= -61.85 to 94.10, p=0.685). Whereas, Thalassemia disease pregnancies had shorter duration of membranes rupture than non-Thalassemia pregnancies. The mean difference was –69.60 minutes (95%CI= -274.56 to 135.37, p=0.505).

Type of membranes rupture: After adjusting for gestational age and underlying diseases of pregnant women, Thalassemia trait pregnancies had high risk for artificial rupture of membranes and leakage of membranes rupture (RR=1.02, 95%CI= 0.52 to 2.02, p=0.949). Whereas, Thalassemia disease pregnancies had low risk (RR=0.98, 95%CI= 0.15 to 6.40, p=0.979).

Amniotic fluid: After adjusting for gestational age and first stage of labour, Thalassemia trait and Thalassemia disease pregnancies had risk of abnormal amniotic fluid (RR=1.53, 95%CI= 0.91 to 2.55, p=0.111 and RR=1.44, 95%CI= 0.35 to 5.95, p=0.618).

Mode of delivery: After adjusting for gestational age, complication during pregnancy and birth weight, Thalassemia trait and in Thalassemia disease pregnancies had low risk for abnormal delivery (RR=0.91, 95%CI= 0.67 to 1.23, p=0.550 and RR=0.23, 95%CI= 0.03 to 1.53, p=0.129).

Indications for abnormal delivery: After adjusting for gestational age, complication during pregnancy and birth weight, Thalassemia trait and Thalassemia disease pregnancies had low risk for having indications for abnormal delivery (RR=0.97, 95%CI= 0.73 to 1.29, p=0.815 and RR=0.22, 95%CI= 0.03 to 1.48, p=0.120).

First stage of labour: After adjusting for age, gravida, birth weight and duration of membranes rupture, Thalassemia trait and Thalassemia disease pregnancies had longer first stage of labour than non-Thalassemia pregnancies. The differences were 9.05 minutes (95%CI= -25.18 to 43.28, p=0.603) and 11.93 minutes (95%CI= -77.17 to 101.03, p=0.792).

Second stage of labour in nullipara group: After adjusting for age, placenta characteristics, gestational age and complication during pregnancy, Thalassemia trait and Thalassemia disease pregnancies had shorter second stage of labour than non-Thalassemia pregnancies. The differences were -0.91 minutes (95%CI= -8.84 to 7.03, p=0.822) in Thalassemia trait and –0.73 minutes (95%CI= -17.63 to 16.17, p=0.932) in Thalassemia disease.

Second stage of labour in multipara group: After adjusting for age, placenta characteristics, gestational age and complication during pregnancy, the second stage of labour in Thalassemia trait and Thalassemia disease pregnancies was longer than non-Thalassemia pregnancies, the mean differences were 2.98 minutes (95%CI= -1.69 to 7.64, p=0.210) and 3.62 minutes (95%CI= -11.68 to 18.92, p=0.641), respectively.

Prolonged 2nd stage in nullipara: After adjusting for age, placenta characteristics, gestational age and complication during pregnancy, the Thalassemia trait pregnancies had low risk for prolonged 2nd stage (RR=0.50, 95%CI= 0.14 to 1.73, p=0.274). Whereas, the Thalassemia disease pregnancies had risk for prolonged 2nd stage (RR=1.02, 95%CI= 0.13 to 7.74, p=0.986).

Prolonged 2nd stage in multipara: After adjusting for age, placenta characteristics, gestational age and complication during pregnancy, Thalassemia trait and Thalassemia disease pregnancies had risk for prolonged 2nd stage (RR=1.87, 95%CI= 0.97 to 3.62, p=0.062 and RR= 2.07, 95%CI= 0.27 to 15.71, p=0.483, respectively).

Third stage of labur: After adjusting for age, placenta characteristics, gestational age and complication during pregnancy, Thalassemia trait and Thalassemia disease pregnancies had shorter third stage of labour than non-Thalassemia pregnancies. The differences were –0.69 minutes (95%CI= -2.12 to 0.73, p=0.340) and –0.07 minutes (95%CI= -3.55 to 3.41, p=0.967), respectively.

Prolonged 3rd stage in multipara: After adjusting for age, placenta characteristics, gestational age and complication during pregnancy, the Thalassemia trait pregnancies had low risk of prolonged 3rd stage (RR=0.39, 95%CI= 0.05 to 3.23, p=0.365). Whereas, the Thalassemia disease pregnancies had high risk of prolonged 3rd stage (RR=3.29, 95%CI= 0.43 to 25.40, p=0.236).

Blood loss: After adjusting for parity, mode of delivery, duration of labour, birth weight and placenta weight, Thalassemia trait and Thalassemia disease pregnancies had amount of blood loss more than non-Thalassemia pregnancies. The mean differences were 0.77 cc. (95%CI= -20.62 to 22.16, p=0.943) and 7.30 cc. (95%CI= -46.07 to 60.66, p=0.788), respectively.

Postpartun hemorrhage (PPH): After adjusting for parity, mode of delivery, duration of labour, birth weight and placenta weight, Thalassemia trait and Thalassemia disease pregnancies had risk of PPH (RR=1.36, 95%CI= 0.46 to 4.05, p=0.582 and RR= 2.72, 95%CI= 0.34 to 21.45, p=0.343, respectively).

Placenta weight: After adjusting for gestational age, HIV infection and VDRL infection, the Thalassemia trait pregnancies had less placenta weight than the non-Thalassemia pregnancies. The mean difference was –2.33 gm. (95%CI= -27.39 to 22.72, p=0.855). Whereas, the Thalassemia disease pregnancies had more placenta weight than non-Thalassemia pregnancies. The mean difference was 1.06 gm. (95%CI= -72.01 to 74.14, p=0.977).

Cord length: After adjusting for gestational age, Thalassemia trait and Thalassemia disease pregnancies had more cord length than non-Thalassemia pregnancies. The differences were 0.37 cm. (95%CI= -1.67 to 2.41, p=0.723) and 7.69 cm. (95%CI= 2.20 to 13.19, p=0.006), respectively.

Placenta characteristics: After adjusting for gestational age and complication during pregnancy, the Thalassemia trait pregnancies had low risk of abnormal placenta characteristics (RR=0.91, 95%CI= 0.24 to 3.36, p=0.883). Whereas, the Thalassemia disease pregnancies had high risk of abnormal placenta characteristics (RR=3.07, 95%CI= 0.41 to 22.74, p=0.273).

Table 12 Multivariate analysis for obstetrics outcome, mean difference or risk ratio, 95% limit and p-value.

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Membranes rupture before delivery [#a]								
	0.74	0.44	1.27	0.281	0.45	0.07	2.97	0.404
Duration of membranes rupture(min.)[@b]								
	16.13	-61.85	94.10	0.685	-69.60	-274.56	135.37	0.505
Type of membranes rupture [c]	[#] 1.02	0.52	2.02	0.949	[&]0.98	0.15	6.40	0.979
Amniotic fluid [#d]	1.53	0.91	2.55	0.111	1.44	0.35	5.95	0.618
Mode of delivery [#e]	0.91	0.67	1.23	0.550	0.23	0.03	1.53	0.129
Indication for abnormal delivery [#e]	0.97	0.73	1.29	0.815	0.22	0.03	1.48	0.120

[@] mean difference

[#] risk ratio

[&] estimate risk ratio

[a] adjusted for gestational age, occupation

[b] adjusted for gestational age

[c] adjusted for gestational age, underlying disease of pregnant women

[d] adjusted for gestational age, first stage of labour

[e] adjusted for gestational age, complication during pregnancy, birth weight

Table 12 Multivariate analysis for obstetrics outcome, mean difference or risk ratio, 95% limit and p-value (continued).

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
First stage of labour (min.) [@a]	9.05	-25.18	43.28	0.603	11.93	-77.17	101.03	0.792
Second stage of labour (min.) [@a]								
Nullipara	-0.91	-8.84	7.03	0.822	-0.73	-17.63	16.17	0.932
Multipara	2.98	-1.69	7.64	0.210	3.62	-11.68	18.92	0.641
Prolonged 2nd stage [#a]								
Nullipara	0.50	0.14	1.73	0.274	1.02	0.13	7.74	0.986
Multipara	1.87	0.97	3.62	0.062	2.07	0.27	15.71	0.483
Third stage of labour (min.) [@b]	-0.69	-2.12	0.73	0.340	-0.07	-3.55	3.41	0.967
Prolonged 3rd stage [&b]	0.39	0.05	3.23	0.365	3.29	0.43	25.40	0.236

[@] mean difference

[#] risk ratio

[&] estimate risk ratio

[a] adjusted for age, gravida, birth weight, duration of membranes rupture

[b] adjusted for age, placenta weight, placenta characteristics, gestational age, complication during pregnancy

Table 12 Multivariate analysis for obstetrics outcome, mean difference or risk ratio, 95% limit and p-value (continued).

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Blood loss (cc.) [@a]	0.77	-20.62	22.16	0.943	7.30	-46.07	60.66	0.788
PPH [#a]	1.36	0.46	4.05	0.582	2.72	0.34	21.45	0.343
Placenta weight (gm.) [@b]	-2.33	-27.39	22.72	0.855	1.06	-72.01	74.14	0.977
Cord length (cm.) [@c]	0.37	-1.67	2.41	0.723	7.69	2.20	13.19	0.006
Placenta characteristics [#d]	0.91	0.24	3.36	0.883	3.07	0.41	22.74	0.273

[@] mean difference

[#] risk ratio

[a] adjusted for parity, mode of delivery, duration of labour, birth weight, placenta weight

[b] adjusted for gestational age, HIV infection, VDRL infection

[c] adjusted for gestational age

[d] adjusted for gestational age, complication during pregnancy

4.4 Multivariate analysis of outcomes of neonatal in Thalassemia and non-Thalassemia mothers is shown in table 13.

Birth weight: After adjusting for age, complication during pregnancy, gestational age, body mass index, maternal weight gain and gravida, the babies born to Thalassemia trait and Thalassemia disease mothers had lower birth weight than babies born to non-Thalassemia mothers. The differences were –15.77 gm. (95%CI= -96.49 to 64.94, p=0.701) and –364.18 gm. (95%CI= -584.85 to -143.50, p=0.001), respectively.

Low birth weight infant (LBW): After adjusting for age, complication during pregnancy, gestational age, body mass index, maternal weigh gain and gravida, Thalassemia trait and Thalassemia disease mothers had high risk of LBW infant (RR=1.45, 95%CI= 0.63 to 3.35, p=0.383 and RR=9.26, 95%CI= 2.92 to 29.35, p<0.001, respectively).

Birth length: After adjusting for age, complication during pregnancy, gestational age, body mass index, maternal weight gain and gravida, the birth lengths of babies born to Thalassemia trait and Thalassemia disease mothers were shorter than those of babies born to non-Thalassemia mothers. The differences were –0.36cm. (95%CI= -0.88 to 0.17, p=0.182 and –1.85 cm. (95%CI= -3.33 to –0.37, p=0.014, respectively).

Head circumference: After adjusting for age, complication during pregnancy, gestational age, body mass index, maternal weight gain and gravida, the babies of Thalassemia trait mothers had longer head circumference than babies of non-Thalassemia mothers. The mean difference was 0.18 cm. (95%CI= -0.11 to 0.46,

p=0.223). Whereas, babies of Thalassemia disease mothers had smaller head size than babies of non-Thalassemia mothers. The significant difference was –1.26 cm. (95%CI= -2.12 to –0.39, p=0.004).

Apgar score at 1 minute: After adjusting for complication during pregnancy, gestational age, duration of labour and birth weight, the babies of Thalassemia trait mothers had higher Apgar score at 1 minute than babies of non-Thalassemia mothers. A significant difference was 0.24 score (95%CI= 0.03 to 0.45, p=0.025). Whereas, babies of Thalassemia disease mothers had lower Apgar score at 1 minute than babies of non-Thalassemia mothers. The mean difference was –0.29 score (95%CI= -0.82 to 0.24, p=0.288).

Apgar score at 5 minutes: After adjusting for complication during pregnancy, gestational age, duration of labour and birth weight, the babies of Thalassemia trait mothers had higher Apgar score at 5 minutes than babies of non-Thalassemia mothers. A significant difference was 0.20 score (95%CI= 0.03 to 0.37, p=0.021). Whereas, babies of Thalassemia disease mothers had lower Apgar score at 5 minutes than babies of non-Thalassemia mothers, the mean difference was –0.13 score (95%CI= -0.56 to 0.31, p=0.565).

Congenital anomaly: After adjusting for underlying disease of pregnant women, babies of Thalassemia trait and Thalassemia disease mothers had high risk of congenital anomaly (RR=4.83, 95%CI= 0.44 to 52.85, p=0.197 and RR=24.54, 95%CI= 1.62 to 370.93, p=0.021, respectively).

Cord coiling: After adjusting for birth weight and cord length, the babies born to Thalassemia trait mothers was less cord coiling than babies born to non-Thalassemia mothers, the difference was –0.01 round (95%CI= -0.10 to 0.09, p=0.916). Whereas, babies born to Thalassemia disease mothers had hypercoiled cord than babies born to non-Thalassemia mothers. The mean difference was 0.38 round (95%CI= 0.12 to 0.64, p=0.004).

Birth complication: After adjusting for mode of delivery, membranes rupture before delivery, and prolonged second stage, the babies of Thalassemia trait and Thalassemia disease mothers had risk of birth complication (RR=1.37, 95%CI= 0.91 to 2.07, p=0.127 and RR=1.92, 95%CI= 0.82 to 4.52, p=0.133, respectively).

Table 13 Multivariate analysis for neonatal outcome, mean difference or risk ratio, 95% limit and p-value.

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Birth weight (gm.) [@a]	-15.77	-96.49	64.94	0.701	-364.18	-584.85	-143.50	0.001
Low birth weight infant [#a]	1.45	0.63	3.35	0.383	9.26	2.92	29.35	<0.001
Birth length (cm.) [@a]	-0.36	-0.88	0.17	0.182	-1.85	-3.33	-0.37	0.014
Head circumference (cm.) [@a]	0.18	-0.11	0.46	0.223	-1.26	-2.12	-0.39	0.004
Apgar score at 1 minutes [@b]	0.24	0.03	0.45	0.025	-0.29	-0.82	0.24	0.288
Apgar score at 5 minutes [@b]	0.20	0.03	0.37	0.021	-0.13	-0.56	0.31	0.565
Congenital anomaly [#c]	4.83	0.44	52.85	0.197	24.54	1.62	370.93	0.021
Cord coiling [@d]	-0.01	-0.10	0.09	0.916	0.38	0.12	0.64	0.004
Birth complication [#e]	1.37	0.91	2.07	0.127	1.92	0.82	4.52	0.133

[@] mean difference

[#] risk ratio

[a] adjusted for age, complication during pregnancy, gestational age, body mass index, maternal weight gain, gravida

[b] adjusted for complication during pregnancy, gestational age, duration of labour, birth weight

[c] adjusted for underlying disease of pregnant women

[d] adjusted for birth weight, cord length

[e] adjusted for mode of delivery, membranes rupture before delivery, prolonged second stage

5. Maternal and neonatal postpartum follow up

5.1 Postpartum maternal characteristics are shown in table 14.

Puerperium infection: The percentages of puerperium infection among the three groups were statistically different (p=0.001): 4.4% in non-Thalassemia, 12.9% Thalassemia trait, and 23.1% Thalassemia disease.

Maternal last status: All subjects were alive after the delivery.

Abnormal conditions at discharge: Only 1.5 % of the Thalassemia trait mothers had fever.

Duration of hospitalization: The average of duration of hospitalization was 4.26 (SD=2.11) in non-Thalassemia mothers, 4.27 (SD=2.21) in Thalassemia trait mothers, and 4.85 (SD=2.30) in Thalassemia disease mothers. The differences were not statistically significant (p=0.607).

Table 14 Maternal postpartum characteristics of subjects classified by thalassemia.

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	N=132	%	n=13	%	
Puerperium infection							
No	305	95.6	115	87.1	10	76.9	0.001
Yes	14	4.4	17	12.9	3	23.1	
Maternal last status							
Alive	319	100.0	132	100.0	13	100.0	
Dead	0	0.0	0	0.0	0	0.0	
Abnormal conditions at discharge							
Normal	319	100.0	130	98.5	13	100.0	0.136
Fever	0	0.0	2	1.5	0	0.0	
Duration of hospitalization							
1 – 3	155	48.6	70	53.0	6	46.1	0.643
4 – 7	141	44.2	53	40.2	5	38.5	
8 – 14	23	7.2	9	6.8	2	15.4	
Mean (SD)	4.26	(2.11)	4.27	(2.21)	4.85	(2.30)	0.607[a]
Range	2 – 13		2 - 14		2 - 9		

* Exact probability test [a] Kruskal – Wallis test

5.2 Postpartum neonatal characteristics classified by Thalassemia as shown in table 15.

Neonatal morbidity: Most of the babies had no neonatal morbidity: 95.9% in non-Thalassemia mothers, 91.7% in Thalassemia trait mothers, and 92.3% in Thalassemia disease mothers. The rest had birth asphyxia, transient tachypnea, anemia, respiratory distress syndrome, and skin infection. The differences were not statistically significant. 3.8% of babies born to Thalassemia trait mothers had G6PD deficiency.

Fever within 7 days: Most of the babies had no fever within 7 days of birth: 86.2% in non-Thalassemia mothers, 77.3% in Thalassemia trait mothers, and 76.9% in Thalassemia disease mothers. The differences among these groups were statistically significant (p=0.044).

Neonatal jaundice within 7 days in low birth weight infant: Most of the babies had jaundice within 7 days of birth: 87.5% in non-Thalassemia mothers, 100.0% in Thalassemia trait mothers, and 100.0% in Thalassemia disease mothers. The differences among these groups were not statistically significant (p=1.000).

Bilirubin level within 7 days in low birth weight infant: Average bilirubin of the babies was 14.64 mg.% (SD=2.27) in non-Thalassemia mothers, 20.1 mg.% (SD=0.57) in Thalassemia trait mothers, and 14 mg.% (SD=1.0) in Thalassemia disease mothers. The difference among these groups were not statistically significant (p=0.095).

Neonatal jaundice within 7 days in normal weight infant: Most of the babies had jaundice within 7 days: 64.4% in non-Thalassemia mothers, 53.2% in Thalassemia trait mothers, and 60.0% in Thalassemia disease mothers. The differences among these groups were not statistically significant (p=0.389).

Bilirubin level within 7 days in normal weight infant: The average bilirubin of the babies was 15.17 mg.% (SD=2.52) in non-Thalassemia mothers, 15.57 mg.% (SD=4.13) in Thalassemia trait mothers, and 15.44 mg.% (SD=3.15) in Thalassemia disease mothers. The differences were not statistically significant (p=0.937).

Neonatal jaundice after 7 days in low birth weight infant: Most of the babies in this study had no jaundice after 7 days: 99.7% in non-Thalassemia mothers, 100.0% in Thalassemia trait mothers, and 100.0% in Thalassemia disease mothers. The differences among these groups were not statistically significant (p=1.000).

Hematocrit level within 7 days: The average hematocrit level within 7 days of babies was 56.36 % (SD=5.53) in non-Thalassemia mothers, 53.18 % (SD=6.39) in Thalassemia trait mothers, and 55.46 % (SD=5.45) in Thalassemia disease mothers. The differences were statistically significant (p=0.001). According to the categorization of hematocrit levels into anemia, normal, and polycythemia, these three groups were not different (p=0.161).

Hematocrit level 7-28 days: The average hematocrit level 7-28 days old babies was 52.70 % (SD=3.37) in non-Thalassemia mothers, 44.91 % (SD=5.22) in Thalassemia

trait mothers, and 49.0 % (SD=1.0) in Thalassemia disease mothers. The differences were statistically significant (p=0.005).

Neonatal last status: All of the babies were alive.

Abnormal conditions at discharge or referral: Most of the babies had no untreated conditions at discharge or referral: 97.5% in non-Thalassemia mothers, 93.2% in Thalassemia trait mothers, and 92.3% in Thalassemia disease mothers. The rest had fever, jaundice, birth asphyxia, respiratory failure, and skin infection. The differences among these groups were not statistically significant. However, the percentage of birth anomaly of babies in Thalassemia disease was statistically high (p=0.034).

Duration of hospitalization : The average of duration of hospitalization was 4.47 (SD=2.74) in babies of non-Thalassemia mothers, 4.34 (SD=2.27) in those of Thalassemia trait mothers, and 5.23 (SD=3.42) in those of Thalassemia disease mothers. The differences among these groups were not statistically significant (p=0.772).

Table 15 Neonatal postpartum characteristics of subjects classified by thalassemia.

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Neonatal morbidity							
No	306	95.9	121	91.7	12	92.3	0.141
Yes	13	4.1	11	8.3	1	7.7	
Birth asphyxia	7	2.2	2	1.5	1	7.7	0.313
Transient trachypnea	3	0.9	2	1.5	0	0.0	0.682
G6PD	0	0.0	5	3.8	0	0.0	0.005
Anemia	0	0.0	2	1.5	0	0.0	0.137
Respiratory distress syndrome	1	0.3	0	0.0	0	0.0	1.000
Skin infection	2	0.6	0	0.0	0	0.0	1.000
Fever within 7 days							
No	275	86.2	102	77.3	10	76.9	0.044
Yes	44	13.8	30	22.7	3	23.1	

* Exact probability test

Table 15 Neonatal postpartum characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Neonatal jaundice within 7 days in low birth weight infant							
No	1	12.5	0	0.0	0	0.0	1.000
Yes	7	87.5	2	100.0	3	100.0	
Bilirubin level within 7 days in low birth weight infant (mg.%)							
6 – 12	1	12.5	0	0.0	0	0.0	0.124
12.1 – 17.9	6	75.0	0	0.0	3	100.0	
≥ 18	1	12.5	2	100.0	0	0.0	
Mean (SD)	14.64	(2.27)	20.1	(0.57)	14	(1.0)	0.095[a]
Range	11.8 - 18.7		19.7 - 20.5		13.0 – 15.0		
Neonatal jaundice within 7 days in normal weight infant							
No	37	35.6	22	46.8	2	40.0	0.389
Yes	67	64.4	25	53.2	3	60.0	

* Exact probability test [a] Kruskal – Wallis test

Table 15 Neonatal postpartum characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Bilirubin level within 7 days in normal weight infant (mg.%)							
7 – 14	37	35.6	22	46.8	2	40.0	0.114
14.1 – 19.9	61	58.6	18	38.3	3	60.0	
≥ 20	6	5.8	7	14.9	0	0.0	
Mean (SD)	15.17	(2.52)	15.57	(4.13)	15.44	(3.15)	0.937[a]
Range	9.4 - 22.5		7.7 - 31.2		11.9 - 19.7		
Neonatal jaundice after 7 days in low birth weight infant							
No	318	99.7	132	100.0	13	100.0	1.000
Yes	1	0.3	0	0.0	0	0.0	
Hematrocrit level within 7 days (%)							
Anemia	0	0.0	1	1.1	0	0.0	0.161
Normal	178	92.7	87	96.7	11	100.0	
Polycythemia	14	7.3	2	2.2	0	0.0	
Mean (SD)	56.36	(5.53)	53.18	(6.39)	55.46	(5.45)	0.001[a]
Range	42 - 70		37 - 65		45 - 63		

* Exact probability test [a] Kruskal – Wallis test

Table 15 Neonatal postpartum characteristics of subjects classified by thalassemia (continued).

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Hematocrit level 7 – 28 days							
Mean (SD)	52.70	(3.37)	44.91	(5.22)	49	(1.0)	0.005[a]
Range	48 - 58		37 - 52		49 - 49		
Neonatal last status							
Alive	319	100.0	131	99.2	13	100.0	0.313
Dead	0	0.0	1	0.8	0	0.0	
Abnormal conditions at discharge or referral							
Normal	311	97.5	123	93.2	12	92.3	0.058
Abnormal	8	2.5	9	6.8	1	7.7	
Fever	0	0.0	2	1.5	0	0.0	0.137
Jaundice	5	1.6	2	1.5	0	0.0	1.000
Birth asphyxia	1	0.3	0	0.0	0	0.0	1.000
Fever and jaundice	0	0.0	1	0.8	0	0.0	0.314
Respiratory failure	0	0.0	1	0.8	0	0.0	0.314

* Exact probability test [a] Kruskal – Wallis test

Table 15 Neonatal postpartum characteristics of subjects classified by thalassemia (continued).

Characteristics	Thalassemia						p-value*
	Normal		Trait		Disease		
	n=319	%	n=132	%	n=13	%	
Anemia	0	0.0	1	0.8	0	0.0	0.314
Skin infection	1	0.3	0	0.0	0	0.0	0.314
Anomaly	1	0.3	2	1.5	1	7.7	0.034
Duration of hospitalization							
1 – 3	149	46.7	68	51.5	6	46.1	0.761
4 – 7	143	44.9	54	40.9	5	38.5	
8 – 14	25	7.8	10	7.6	2	15.4	
≥ 15	2	0.6	0	0.0	0	0.0	
Mean (SD)	4.47	(2.74)	4.34	(2.27)	5.23	(3.42)	0.772[a]
Range	2 - 31		1 - 14		2 - 14		

* Exact probability test [a] Kruskal – Wallis test

5.3 Multivariate analysis of outcomes of postpartum in Thalassemia and non-Thalassemia pregnancies is shown in table 16.

Puerperium infection: After adjusting for mode of delivery, gestational age, indication for abnormal delivery and type of membrane rupture, Thalassemia trait and Thalassemia disease mothers had high risk of puerperium infection (RR=2.98, 95%CI= 1.47 to 6.06, p=0.002, and RR=5.42, 95%CI= 1.55 to 18.88, p=0.008, respectively).

Abnormal conditions at discharge: Thalassemia trait and Thalassemia disease mothers had 4.83 and 24.54 times of abnormal conditions at discharge compared to non-Thalassemia mothers (RR=4.83, 95%CI= 0.44 to 52.85, p=0.153, and RR=24.54, 95%CI= 1.62 to 370.93, p<0.001, respectively).

Duration of hospitalization: The duration of hospitalization in Thalassemia trait and Thalassemia disease mothers were longer than those of non-Thalassemia mothers. The differences were 0.01 days (95%CI= -0.43 to 0.44, p=0.971), and 0.59 days (95%CI= -0.60 to 1.78, p=0.332), respectively.

Table 16 Multivariate analysis for maternal postpartum follow up, mean difference or risk ratio, 95% limit and p-value.

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Puerperium infection [#a]	2.98	1.47	6.06	0.002	5.42	1.55	18.88	0.008
Abnormal conditions at discharge [&]	4.83	0.44	52.85	0.153	24.54	1.62	370.93	<0.001
Duration of hospitalization [@]	0.01	-0.43	0.44	0.971	0.59	-0.60	1.78	0.332

[@] mean difference

[#] risk ratio

[a] adjusted for mode of delivery, gestational age, indication for abnormal delivery, type of membranes rupture

5.4 Multivariate analysis for outcome of postpartum neonatal in Thalassemia and non-Thalassemia pregnancies is shown in table 17.

Neonatal morbidity: After adjusting for geststional age, placenta weight and prolonged second stage, the babies born to Thalassemia trait and Thalassemia disease mothers had risk of neonatal morbidity (RR=2.14, 95%CI= 0.89 to 5.16, p=0.090, and RR=1.15, 95%CI= 0.14 to 9.33, p=0.897, respectively).

Fever within 7 days: After adjusting for gestational age, birth weight and G6PD deficiency, the babies born to Thalassemia trait and Thalassemia disease mothers had risk of fever within 7 days of birth (RR=1.65, 95%CI= 1.09 to 2.50, p=0.019), and RR=1.67, 95%CI= 0.60 to 4.68, p=0.327, respectively).

Jaundice within 7 days in low birth weight infant: After adjusting for gestational age, birth weight and G6PD deficiency, the babies born to Thalassemia trait and Thalassemia disease mothers had risk of jaundice within 7 days (RR=1.16, 95%CI= 0.24 to 5.63, p=0.851, and RR=1.18, 95%CI= 0.26 to 5.39, p=0.829, respectively).

Bilirubin level within 7 days in low birth weight infant: After adjusting for gestational age, birth weight and G6PD deficiency, the babies born to Thalassemia trait mothers had higher bilirubin level within 7 days than babies born to non-Thalassemia mothers, a significant difference was 5.46 mg.% (95%CI= 2.22 to 8.92, p=0.006). Whereas, babies born to Thalassemia disease mothers had lower bilirubin level within 7 days than babies born to non-Thalassemia mothers, the mean difference was –0.64 mg.% (95%CI= -3.59 to 2.32, p=0.642).

Jaundice within 7 days in normal weight infant: After adjusting for gestational age, birth weight and G6PD deficiency, the babies born to Thalassemia trait and Thalassemia disease mothers had low risk of jaundice within 7 days (RR=0.83, 95%CI= 0.52 to 1.31, p=0.414, and RR=0.93, 95%CI= 0.29 to 2.96, p=0.904, respectively).

Bilirubin level within 7 days in normal weight infant: After adjusting for gestational age, birth weight and G6PD deficiency, the bilirubin level within 7 days in babies born to Thalassemia trait and Thalassemia disease mothers were higher than babies born to non-Thalassemia mothers, the mean differences were 0.40 mg.% (95%CI= -0.68 to 1.47, p=0.470), and 0.27 mg.% (95%CI= -2.54 to 3.08, p=0.850), respectively.

Anemia within 7 days: After adjusting for gestational age, birth weight, complication during pregnancy and G6PD deficiency, the babies born to Thalassemia trait and Thalassemia disease mothers had risk of anemia within 7 days (RR= 2.13, 95%CI= 0.13 to 33.72, p=0.582, and RR=17.45, 95%CI= 1.17 to 260.86, p=0.005, respectively).

Hematocrit level within 7 days: After adjusting for gestational age, birth weight complication during pregnancy and G6PD deficiency, the babies born to Thalassemia trait and Thalassemia disease mothers had lower hematocrit level within 7 days than the babies born to non-Thalassemia mothers, the mean differences were –3.01 %

(95%CI= -4.50 to –1.52, p<0.001), and –0.67 % (95%CI= -4.27 to 2.93, p=0.766), respectively.

Hematocrit level after 7 days: After adjusting for gestational age, birth weight complication during pregnancy and G6PD deficiency, the babies born to Thalassemia trait and Thalassemia disease mothers had lower hematocrit level after 7 days than the babies born to non-Thalassemia mothers, the mean differences were –7.00 % (95%CI= -11.38 to –2.62, p=0.004), and –0.48 % (95%CI= -11.49 to 10.53, p=0.928), respectively.

Abnormal conditions at discharge and referral: After adjusting for gestational age, underlying disease of pregnant women, and birth weight, the babies born to Thalassemia trait and Thalassemia disease mothers had increased risk of untreated conditions at discharge or referral (RR=2.67, 95%CI= 1.03 to 6.97, p=0.044, and RR=1.96, 95%CI= 0.24 to 16.29, p=0.534, respectively).

Duration of hospitalization: Duration of hospitalization in the babies born to Thalassemia trait mothers was shorter than babies born to non-Thalassemia mothers, the mean difference was –0.13 day (95%CI= -0.67 to 0.40, p=0.628). Whereas, babies born to Thalassemia disease mothers had longer than babies born to non-Thalassemia mothers, the mean difference was 0.76 day (95%CI= -0.71 to 2.22, p=0.311).

Table 17 Multivariate analysis for neonatal postpartum follow up, mean difference or risk ratio, 95% limit and p-value.

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Neonatal morbidity [#a]	2.14	0.89	5.16	0.090	1.15	0.14	9.33	0.897
Fever in 7 days [#b]	1.65	1.09	2.50	0.019	1.67	0.60	4.68	0.327
Jaundice within 7 days in Low birth weight infant [#b]	1.16	0.24	5.63	0.851	1.18	0.26	5.39	0.829
Bilirubin level within 7 days in Low birth weight infant (mg.%) [@b]	5.46	2.22	8.92	0.006	-0.64	-3.59	2.32	0.642
Jaundice within 7 days in normal weight infant [#b]	0.83	0.52	1.31	0.414	0.93	0.29	2.96	0.904
Bilirubin level within 7 days in normal weight infant (mg.%) [@b]	0.40	-0.68	1.47	0.470	0.27	-2.54	3.08	0.850

[@] mean difference

[#] risk ratio

[a] adjusted for gestational age, placenta weight, prolonged second stage

[b] adjusted for gestational age, birth weight, G6PD deficiency

Table 17. Multivariate analysis for neonatal postpartum follow up, mean difference or risk ratio, 95% limit and p-value (continued).

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Anemia within 7 days [a]	[#]2.13	0.13	33.72	0.582	[&]17.45	1.17	260.86	0.005
Hematocrit level in 7 days (%) [@a]	-3.01	-4.50	-1.52	<0.001	-0.67	-4.27	2.93	0.766
Hematocrit level after 7 days (%) [@a]	-7.00	-11.38	-2.62	0.004	-0.48	-11.49	10.53	0.928
Abnormal conditions at discharge and referral [#b]	2.67	1.03	6.94	0.044	1.96	0.24	16.29	0.534
Duration of hospitalization	-0.13	-0.67	0.40	0.628	0.76	-0.71	2.22	0.311

[@] mean difference

[#] risk ratio

[&] estimate risk ratio

[a] adjusted for gestational age, birth weight, complication during pregnancy, G6PD deficiency

[b] adjusted for gestational age, underlying disease of pregnant women, birth weight

Effect of Thalassemia on pregnancy outcome

The differences of important characteristics among these three groups which were statistically significant as shown in table 18.

1. Pregnancy outcome

1.1 Reproductive characteristics showed that history of abortion in non-Thalassemia pregnancies was 18.9% which was less than those of Thalassemia trait pregnancies (25.8%) and those of Thalassemia disease pregnancies (23.1%) (p=0.010).

1.2 Pregnancy progression

The Hct levels at 1st visit of ANC of Thalassemia trait and Thalassemia disease pregnancies were lower than that of non-Thalassemia pregnancies (mean difference = -1.69%, 95%CI = -2.35 to –1.03 and -3.4%, 95%CI = -5.39 to –1.52 respectively).

The Hct levels at 3rd trimester of Thalassemia trait and Thalassemia disease pregnancies were lower than that of non-Thalassemia pregnancies (mean difference = -1.92%, 95%CI = -2.75 to –1.09 and -1.99%, 95%CI = -3.96 to –0.02, respectively).

1.3 Pregnancy outcome: Most of the subjects among these three groups were similar including gestational age, membranes rupture before delivery, type of membranes rupture, amniotic fluid, mode of delivery, blood loss, placenta weight and placenta characteristics. Only the cord length of Thalassemia disease pregnancies was longer than that of non-Thalassemia pregnancies (mean difference = 7.69 cm., 95%CI = 2.20 to 13.19), whereas cord length of Thalassemia trait pregnancies was not statistically significant (mean difference= 0.37cm. 95%CI = -1.67 to 2.41).

1.4 Postpartum maternal outcome showed Thalassemia disease and Thalassemia trait mothers had high risk of puerperium infection (RR=5.42, 95%CI=1.55 to 18.88 and RR= 2.98, 95%CI= 1.47 to 6.06, respectively).

2. Outcome of babies born to mothers among these three groups

2.1 Neonatal outcome

2.1.1 The babies born to Thalassemia disease mothers had high risk of low birth weight infant (RR=9.26, 95%CI=2.92 to 29.35), whereas babies born to Thalassemia trait mothers did not show statistically difference (RR= 1.45, 95%CI= 0.63 to 3.35).

2.1.2 The average of birth length of babies born to Thalassemia disease mothers was shorter than non-Thalassemia mothers (mean difference = -1.85 cm., 95%CI=-3.33 to –0.37), whereas babies born to Thalassemia trait mothers did not show statistically difference (mean difference= -0.36 cm., 95%CI= -0.88 to 0.17).

2.1.3 The average of head circumference of babies born to Thalassemia disease mothers was shorter than non-Thalassemia mothers (mean difference = -1.26 cm., 95%CI=-2.12 to –0.39), whereas babies born to Thalassemia trait mothers did not show statistically difference (difference = 0.18 cm., 95%CI=-1.11 to 0.46).

2.1.4 The babies born to Thalassemia trait mothers had higher Apgar score at 1 minute than babies born to non-Thalassemia mothers (mean difference = 0.24 score, 95%CI= 0.03 to 0.45), whereas babies born to Thalassemia disease mothers was not statistically significant (mean difference = -0.29, 95%CI= -0.82 to 0.24).

2.1.5 The babies born to Thalassemia trait mothers had higher Apgar score at 5 minutes than babies born to non-Thalassemia mothers (difference = 0.20 score, 95%CI= 0.03 to 0.37) whereas babies born to Thalassemia disease mothers was not statistically significant different (mean difference = -0.13, 95%CI= -0.56 to 0.31).

2.1.6 The babies born to Thalassemia disease mothers had high risk of neonatal anomaly (RR=24.54, 95%CI=1.62 to 370.93), whereas babies born to Thalassemia trait mothers were not statistically significant different (RR= 4.83, 95%CI= 0.44 to 52.85).

2.1.7 The cord coiling of babies born to Thalassemia disease mothers was more than non-Thalassemia mothers (mean difference = 0.38 round, 95%CI=0.12 to 0.64), whereas babies born to Thalassemia trait mothers was not statistically significant (mean difference= -0.01 round, 95%CI= -0.10 to 0.09).

2.2 Postpartum neonatal outcome

2.2.1 The babies born to Thalassemia trait mothers had risk of fever within 7 days (RR=1.65, 95%CI=1.09 to 2.50), whereas babies born to Thalassemia disease mothers was not statistically significant (RR=1.67, 95%CI= 0.60 to 4.68).

2.2.2 LBW infant: The babies of Thalassemia trait mothers had higher bilirubin level than babies to non-Thalassemia mothers (mean difference = 5.46 mg.%, 95%CI= 2.22 to 8.92), whereas babies to Thalassemia disease mothers was not statistically significant (mean difference = -0.64 mg.%, 95%CI= -3.59 to 2.32).

2.2.3 The babies born to Thalassemia trait mothers had lower Hct level within 7 days than that of babies born to non-Thalassemia mothers (mean difference =

-3.01%, 95%CI= -4.50 to –1.52), whereas babies to Thalassemia disease mothers was not statistically significant (mean difference = -0.67, 95%CI= -4.27 to 2.93).

2.2.4 The babies born to Thalassemia trait mothers had lower Hct level after 7 days than that babies born to non-Thalassemia mothers (mean difference = -7.00%, 95%CI= -11.38 to –2.62), whereas babies born to Thalassemia disease mothers was not statistically significant (mean difference = -0.48, 95%CI= -11.49 to 10.53).

2.2.5 The babies born to Thalassemia trait mothers had increased risk of abnormal conditions at discharge or referral (RR=2.67, 95%CI=1.03 to 6.94), whereas babies born to Thalassemia disease mothers had no statistical risk (RR=1.96, 95%CI= 0.24 to 16.29).

Table 18 the effect of thalassemia on pregnancy outcome.

Characteristics	Normal		Thalassemia				p-value*
			Trait		Disease		
	n=319	%	n=132	%	n=13	%	
History of abortion							
No	258	81.1	98	74.2	10	76.9	0.010
1	53	16.7	34	25.8	2	15.4	
2	7	2.2	0	0.0	0	0.0	
3	0	0.0	0	0.0	1	7.7	

* Exact probability test

Table 18 the effect of thalassemia on pregnancy outcome (continued).

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Hematocrit at 1st visit (%) [@a]	-1.69	-2.35	-1.03	<0.001	-3.45	-5.39	-1.52	<0.001
Hematocrit at 3rd trimester(%) [@a]	-1.92	-2.75	-1.09	<0.001	-1.99	-3.96	-0.02	0.047
Cord length (cm.) [@b]	0.37	-1.67	2.41	0.723	7.69	2.20	13.19	0.006
Puerperium infection [#c]	2.98	1.47	6.06	0.002	5.42	1.55	18.88	0.008

[@] mean difference

[#] risk ratio

[a] adjusted for maternal weight gain

[b] adjusted for gestational age

[c] adjusted for mode of delivery, gestational age, indication for abnormal delivery, type of membranes rupture

Table 18 the effect of thalassemia on pregnancy outcome (continued).

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Low birth weight infant [#a]	1.45	0.63	3.35	0.383	9.26	2.92	29.35	<0.001
Neonatal length (cm.) [@a]	-0.36	-0.88	0.17	0.182	-1.85	-3.33	-0.37	0.014
Head circumference (cm.) [@a]	0.18	-0.11	0.46	0.223	-1.26	-2.12	-0.39	0.004
Apgar score at 1 minutes [@b]	0.24	0.03	0.45	0.025	-0.29	-0.82	0.24	0.288
Apgar score at 5 minutes [@b]	0.20	0.03	0.37	0.021	-0.13	-0.56	0.31	0.565
Neonatal anomaly [#c]	4.83	0.44	52.85	0.197	24.54	1.62	370.93	0.021

[@] mean difference

[#] risk ratio

[a] adjusted for age, complication during pregnancy, duration of labour, body mass index, gravida, maternal weight gain

[b] adjusted for complication during pregnancy, gestational age, duration of labour, birth weight

[c] adjusted for underlying disease of pregnant women

Table 18 the effect of thalassemia on pregnancy outcome (continued).

Characteristics	Thalassemia trait				Thalassemia disease			
	Regress coef	95%CI		p-value	Regress coef	95%CI		p-value
Cord coiling [@a]	-0.01	-0.10	0.09	0.916	0.38	0.12	0.64	0.004
Fever within 7 days [#b]	1.65	1.09	2.50	0.019	1.67	0.60	4.68	0.327
Bilirubin within 7 days in BW< 2,500 gm.(mg%) [@b]								
	5.46	2.22	8.92	0.006	-0.64	-3.59	2.32	0.642
Hct within 7 days [@c]	-3.01	-4.50	-1.52	<0.001	-0.67	-4.27	2.93	0.766
Hct 7 – 28 days [@c]	-7.00	-11.38	-2.62	0.004	-0.48	-11.49	10.53	0.928
Abnormal conditions at discharge or referral [#d]								
	2.67	1.03	6.94	0.044	1.96	0.24	16.29	0.534

[@] mean difference

[#] risk ratio

[a] adjusted for placenta weight, cord length

[b] adjusted for gestational age, birth weight, G6PD deficiency

[c] adjusted for complication during pregnancy, gestational age, birth weight, G6PD deficiency

[d] adjusted for underlying disease of pregnant women, gestational age, birth weight

CHAPTER V

DISCUSSION

This retrospective cohort study was performed to evaluate pregnancy outcome in thalassemia. The subjects comprised of 13 cases of Thalassemia disease, 132 cases of Thalassemia trait and 319 cases of non-Thalassemia.

Only 13 cases of Thalassemia disease pregnant women were available to be included in this study. The estimate of Thalassemia in Thai population is 1%, so the number of Thalassemia disease pregnancy was low. In these thirteen cases, one was β-thal/Hb E disease (7.7%), eight were Hemoglobin H disease (61.5%), four were Homozygous Hb E (30.8%). The pateints with Hemoglobin H disease or Homozygous Hb E had varying degree of anemia from mild to moderate that could not represent for severe Thalassemia in pregnant women.

Although severity of Homozygous Hb E is mild, Homozygous Hb E has been defined as a group of Thalassemia disease (63,64). Our Homozygous Hb E cases had the average of hematocrit level of 33.5%, birth weight of 2,887.5 gm, length of newborn of 51.5 cm., and head circumference of 31.38 cm.

DISCUSSION

Mother

History of abortion

Thalassemia trait and Thalassemia disease in pregnant women have higher risk of abortion (25.8% and 23.1%, respectively) than normal women (18.9%) ($p = 0.010$, table 5). Potential hemolysis and low hematocrit level may be the causes of these occurrences. Their fetuses are also having a tendency to have abnormal hemoglobin synthesis (14,26,30).

Weight gain during pregnancy

One hundred and two patients (21.77%) have records of pre-pregnancy weight available, so we analyzed weight gain during pregnancy from these groups only. Average weight gain during pregnancy was 0.31 kg/week in Thalassemia disease, 0.37 kg/week in Thalassemia trait, and 0.40 kg/week in non-Thalassemia pregnancy ($p = 0.429$, table 6). All of these weight gains were below standard of 0.40 – 0.50 kg/week during pregnancy (29). Low weight gain during pregnancy in Thalassemia trait and Thalassemia disease is due to low level of hemoglobin that result in low oxygen and nutrients supply to both mother and fetus (8,30,44).

Hemoglobin level during pregnancy

The average of hematocrit level at first antenatal visit in Thalassemia pregnancy was 33%, significantly lower than the average of normal pregnancy (table 5). In multivariate regression analysis, both Thalassemia trait and Thalassemia disease have significant low hemoglobin and hematocrit concentration compared to normal

pregnancy ($p < 0.001$, table 8). Maternal blood volume starts to increase during the first trimester, expands most rapidly during the second trimester, and then rises at much slower rate during the third trimester to plateau during the last several weeks of pregnancy. This is almost certainly due to a two to threefold increase in maternal plasma erythropoeitin levels (20). Thalassemia trait and Thalassemia disease pregnancy have an abnormality in globin chain synthesis, so they cannot keep the hemoglobin level as the maternal blood volume increases.

Mode of delivery

Mode of delivery among these three groups were similar ($p=0.575$, table 10). The multivariate regression showed that both Thalassemia trait and Thalassemia disease pregnancy had no difference of abnormal delivery compared to normal pregnancy ($p=0.550$ and $p=0.129$ respectively, table 12). In a study from Hongkong, there was no difference in mode of delivery in normal pregnancy and pregnancy with hemoglobin less than 10 mg/dL (27). Given this consistency, mode of delivery would not be affected by anemia.

Premature delivery

Thalassemia trait and Thalassemia disease pregnancy had no difference of premature delivery ($p=0.728$ and $p=0.835$, table 9). Some studies showed that anemia during pregnancy didn't effect to premature delivery (27,39). In contrast, other studies demonstrated higher risk of premature delivery in very low hemoglobin level, especially low hemoglobin level at 5^{th} and 8^{th} month pregnancy (25,33,35,36,37). Our data could not demonstrate this effect because severity of anemia in Thalassemia trait

and disease in our patients was mild. In addition, iron supplement was provided during their pregnancies.

Placenta weight

The mean of placental weight of Thalassemia trait pregnancies was 2.33 gm. (95%CI= -27.39 to 22.72) lower, whereas that of Thalassemia disease pregnancies was 1.06 gm.(95%CI= -72.01 to 74.14) more than non-thalassemia pregnancies (table 12). Some studies reported that placenta size was bigger than normal pregnancy (31,32). However, our finding could not demonstrate the same results because of mild degree of anemia in our Thalassemia pregnancies.

Puerperium infection

Both Thalassemia trait and Thalassemia disease pregnancies had high risk of puerperium infection (RR=2.98, 95%CI= 1.47 to 6.06 and RR=5.42, 95%CI=1.55 to 18.88, respectively, table 16). In many studies, pregnancy with hemoglobin level less than 9 mg/dL had high tendency of infection (25). Anemia has caused low immunity against infections. Therefore, if severe blood loss occurs, patients would have more susceptibility to develop puerperium infection (26,29).

Neonatal

Low birth weight infant

Since birth scores were not available in the medical records, we could not distinguish babies with small for gestational age from this cohort. We can evaluate for low birth weight only. Given our data, the chance of having a low birth weight infant

in Thalassemia disease mothers was 9.26 times (95%CI = 2.92 to 29.35), whereas that of Thalassemia trait mothers was 1.45 times (95%CI = 0.63 to 3.35), but not statistically significant (p=0.383, table13). Many studies of correlation between hemoglobin level during pregnancy and low birth weight infant showed that hemoglobin level less than 10.5 gm% during pregnancy had high correlation to low birth weight infant (36,37,40,41,42,43). In contrast, one study reported no effect of anemia on birth weight (47). Anemia in Thalassemia reduces capacity to carry nutrients and oxygen to maternal and fetal body causing intrauterine growth retardation (8,44,65).

Stillbirth

There was no still birth among all groups of pregnant women participated in this study. This outcome was contrary to some studies conducted in Papua Newguinea. In this study, high still birth rate was about 94 cases to 1,000 birth in low level hemoglobin less than 6 gm/dL. Still birth rates in hemoglobin level 10.0 – 10.9 gm/dL and that more than 11 gm/dL were 14 and 18 cases to 1,000 birth, respectively (41). The other studies showed that hemoglobin level less than 6mg% had high correlation with still birth (48). The above data strongly demonstrated the effect of anemia on still birth. However, our study did not find any correlation between low hemoglobin level and still birth. The reason may be due to good antenatal care for the pregnant women.

Head circumference and length of newborn

In multivariate regression, babies born to Thalassemia disease mothers had smaller head circumference and length than babies born to women without the condition (p=0.014 and p=0.004). Whereas, babies born to Thalassemia trait mothers had no significant difference in terms of head circumference and length compared to babies born to women without the condition (p=0.182 and p=0.223, table 13). In several studies, anemic mothers (hemoglobin level < or = 6.1 g/dl) with low serum ferritin level during pregnancy (serum ferritin level < 10 micrograms / L) had fetal head circumference and length significant less than fetus of normal pregnant mothers (44).

Cord length

The average cord length of babies born to Thalassemia disease mothers was 7.69 cm (p=0.006) longer than those of babies with non-Thalassemia mothers. Whereas the averages of cord length of babaies born to women with Thalassemia trait and non-Thalassemia were similar (p=0.723, table 12). As far as we concern, there was no any study of relationship between anemic pregnancy and cord length available. Our data is the first to demonstrate the relationship between Thalassemia disease pregnancy and cord length of the baby.

Apgar score

The babies born to Thalassemia trait mothers had more Apgar score than babies born to women without the condition (p=0.025). Whereas, babies born to Thalassemia disease mothers had no difference in terms of Apgar score of the babies

born to women without the condition (p=0.288, table13). In the contrary, some studies demonstrated correlation between low hemoglobin level during pregnancy to low Apgar score ($p < 0.001$) (32). The reason of this disagreement is unclear.

Hyperbilirubinemia

In general, the low birth weight infants have low conjugate enzyme level (66). Low birth weight infant in our study had high risk of hyperbilirubinemia. The multivariate regression showed that low birth weight infants born to Thalassemia trait mothers had high hyperbilirubinemia than babies born to non-Thalassemia mothers (p=0.006, table17). Our result was contrast to the report of newborns born to alpha – Thalassemia minor mother in Taipei. The study showed that on day 3 after birth the incidence of hyperbilirubinemia (bilirubin level over 10 mg/dl) was significantly lower in Thalassemia mother than in control group (0.9% vs 9.5%, Fisher's exact probability = 0.0012) (56). Those study included all babies, but our data were analyzed on low birth weight only.

CHAPTER VI

CONCLUSION AND RECOMMENDATION

Conclusion

A retrospective cohort study was conducted at the Mother and Child Hospital Chiang Mai, between 1st December 1997 and 15th June 1999, to evaluate pregnancy outcome of Thalassemia. The total 464 study subjects were comprised of 13 cases of Thalassemia disease, 132 cases of Thalassemia trait, and 319 cases pregnant women without such conditions.

Index groups were defined by purposive sampling from one tube osmotic fragility, dichlorophenol-indophenol and hemoglobin typing. Comparative groups were selected by purposive sampling too. Relevant information was collected from the antenatal care and delivery records. These included demographic character, reproductive character, pregnancy progression, pregnancy outcome, birth outcome and maternal and neonatal postpartum follow-up.

The pregnancy outcome of Thalassemia had significant relation with unfavorable maternal and neonatal outcome. The hematocrit of women with Thalassemia trait and Thalassemia disease was lower than women without the condition. There was no difference of intrapartum obstetric condition among all three groups of women. Thalassemia trait and Thalassemia disease had high risk of puerperium infection.

The outcomes of babies born to Thalassemia disease mothers had more low birth weight, shorter birth length, shorter head size, and neonatal anomaly. In addition, babies born to Thalassemia trait mothers showed more Apgar score at 1, 5 minutes, having fever within 7 days after birth, higher billirubin level within 7 days of birth, less Hct within 7 days, and abnormal condition at discharge or referral.

Recommendation

In the light of these observations, we can thus propose:

1. This study has demonstrated that anemia in Thalassemia trait pregnancies and Thalassemia disease pregnancies have contributed to the increase of maternal and neonatal complications i.e. low birth weight infant, puerperal infection. As mentioned above, surveillance of anemia and anemia prevention care should be more emphasized in antenatal care clinic to decrease morbidity and mortality among the pregnant mothers and infants.

2. Thalassemia prevention and control campaign should be carried out among the fertile and pregnant women to reduce the burden and complications of Thalassemia.

3. Thalassemia trait women should receive more attention from health personnel to promote better women health.

Recommendation for further study

1. Future studies should be considered to confirm the prospective pregnancy outcome of Thalassemia in Thailand

2. Future studies will be required to investigate the association between outcome of Thalassemia and any cause of anemia in pregnancy i.e. iron deficiency.

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APPENDIX

Appendix A

MEDICAL RECORD OF

PREGNANCY OUTCOME OF THALASSEMIA

Identify number_____

(1) Thalassemia pregnant women (0) Normal pregnant women

Hemoglobin typing _____

PART I DEMOGRAPHIC CHARACTERISTIC

1. Name _____ Surname _____ H.N._____
2. Age _____ years. Prepregnancy weight _____ kg Height _____cm.
3. Race

   (1) Thai (2) Other
4. Region

   (1) Buddhist (2) Christian (3) Muslim (4) Other
5. Marital status

   (1) Couple (2) Divorced (3) Separated (4) Widowed
6. Occupation

   (1) House wife (2) Government office (3) Employee

   (4) Official (5) Commercial (6) Agriculture (7) Other
7. Education level

   (1) No education (2) Primary school

   (3) secondary school (4) Diploma / bachelor and higher level

PART II REPRODUCTIVE CHARACTERISTIC

8. LMP_____ EDC _____

9. Gravidity _____ Parity _____ Abortion _____ Living child _____

10. Number of previous preterm delivery _____

11. Number of previous Low Birth Weight delivery _____

12. Family history of illness _____

13. Underlying disease of pregnant women _____

PART III PREGNANCY PROGRESSION

14. Laboratory test for

HIV infection (1) positive (0) negative (.) no test

VDRL (1) positive (0) negative (.) no test

Hepatitis B virus (1) positive (0) negative (.) no test

Hematocrit at first visit _____ % Hematocrit at third trimester _____%

15. Antenatal care visit

No. ANC	Date	BW	BP	Hct	Alb/sug	Edema	Gestation age
1							
2							
3							
4							
5							
6							
delivery							

16. Weight gain during pregnancy _____ kg.

PART IV PREGNANCY OUTCOME AT DELIVERY

17. Birth outcome

(1) Abortion (2) Pre-term birth (3) Term birth (4) still birth

18. Gestational age at delivery _____week

19. Mode of delivery

(1) Normal labor (2) Forceps extraction

(3) Vacuum extraction (4) Cesarean section

due to_____

20. Premature rupture of membrane _____ hours. _____ minutes.

21. Type of rupture of membrane

(1) Spontaneous rupture of membrane (2) Spontaneous leak of membrane

(3) Artificial rupture of membrane (4) Unknown

22. Characteristic of fluid

(1) Clear (2) Mild (3) Moderate (4) Thick (5) Unknown

23. Duration of labour

23.1 First stage of labour _____ hours. _____ minutes.

23.2 Second stage of labour _____ hours. _____ minutes.

23.3 Third stage of labour _____ hours. _____ minutes.

23.4 Total stage of labour _____ hours. _____ minutes.

24. Placenta weight _____ gm.

25. Placenta length _____ cm.

26. Placenta characteristics

(1) Complete (2) Succenturiata placenta (3) Incomplete

(4) Infraction (5) Macerated placenta

27. Estimate blood loss _____ c.c.

28. Primary postpatum hemorrhage

(0) No (1) Yes

PART V POSTPATUM DATA

29. Puerperium infection

(0) No (1) Yes

30. Last status

(1) Dead (date _____) (2) Alive

31. Type of maternal discharge

(0) Normal (1) Abnormal _____

PART VI NEONATAL DATA

32. Infant gender H.N. _____

(1) Male (2) Female

33. Date of birth _____

34. Birth weight _____ gm. Head circumferences _____ cm.

Birth length _____ cm.

35. Birth complication _____

36. Apgar score at 1 minutes. _____. At 5 minutes._____

37. Congenital anomaly

(0) No (1) Yes _____

38. Highest hematocrit level in 7 days _____%

Highest hematocrit level after 7 days _____%

39. Bilirubin level in 7 days _____mg%

Bilirubin level after 7 days _____mg%

40. Neonatal morbidity

	In 24 hours		In 7 days		After 7 days	
Signs and symptom	no	yes	no	yes	no	yes
Fever						
Hyperbilirubinemia						
Anemia						
Other						

41. Last status

(1) Dead (date _____) (2) Alive

42. Type of neonatal discharge

(0) Normal (1) Abnormal _____

Appendix B

Sample size

A retrospective cohort study was look up outcome of thalassemia pregnancy. Although index groups and comparative groups were selected by purposive sampling, the appropriate study size explores the precision of the study. The study size was calculated outcome with cohort study proportion(68).

$$n_1 = \frac{(Z\alpha + Z\beta)^2 \times PQ \times (r+1)}{(P_1+P_O)^2 \times r}$$

$$\overline{P} = \frac{P_1 + rP_O}{1 + r}$$

$$r = \frac{n_O}{n_1}$$

n_1 = number of exposed or number of treatment

n_O = number of non expose or number of control

r = proportion of non-exposed to exposed, or control to treatment

$Z\alpha$ = Standard value from Z table at type I error is α

$Z\beta$ = Standard value from Z table at type II error is β

$\overline{P}$ = Average exposure rate in index group and comparative proup

$\overline{Q}$ = $1 - \overline{P}$

P_1 = Average exposure rate in case

P_O = Average non exposure rate in control

This study for the required total member of pair is: 1:1, set to have 95% confidence level and 80% power of test. When the sample sizes were calculated by

above formula and the various risk factor from literature reviews the sample size in each variable were shown as follow.

- premature delivery

P_I = 0.143 P_O = 0.094

$$n_I = \frac{(1.96 + 0.84)^2 (0.1185 \times 0.8815)2}{0.0024}$$

n_I = 722 n_O = 722

- pre-eclampsia

P_I = 0.40 P_O = 0.05

$$n_I = \frac{(1.96 + 0.84)^2 (0.225 \times 0.775)2}{0.1225}$$

n_I = 27 n_O = 27

- postpartum hemorrhage

P_I = 0.10 P_O = 0.05

$$n_I = \frac{(1.96 + 0.84)^2 (0.075 \times 0.925)2}{0.0025}$$

n_I = 474 n_O = 474

- Low birth weight infant

P_I = 0.409 P_O = 0.105

$$n_I = \frac{(1.96 + 0.84)^2 (0.257 \times 0.743)2}{0.0925}$$

n_I = 38 n_O = 38

BIOGRAPHY

NAME	Miss Paradee Chompookaew
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