To Investigate Pregnancy Outcome of Women with Iron-Deficiency and Beta-Thalassemia in Hong Kong Private Sector

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Abstract

Objective: To investigate the pregnancy outcome of women with beta-thalassemia or iron-deficiency in a private hospital in Hong Kong. **Background:** Beta-thalassemia and iron-deficiency are common diseases worldwide. Defect of haemoglobin synthesis reduces the oxygen carrying capacity of red blood cell and hence increases the risk of fetal hypoxia during pregnancy. Maturation of baby may be affected as a result of preterm birth and low birth weight. **Materials and Methods:** This retrospective, case-control study was performed in Shatin International Medical Centre Union Hospital in Hong Kong SAR, China. Data as collected between 2007 and 2011 from normal pregnant women (n=83), pregnant women with beta-thalassemia (n=63), or with iron-deficiency (n=26) were analyzed. Antenatal screening test was performed to isolate pregnant women according to their low mean corpuscular volume (MCV) (<80 fL) and further to differentiate them into beta-thalassemia group and iron-deficiency group by their haemoglobin pattern and ferritin level. The gestational age (preterm birth: <37 weeks), birth weight (low: <2.5 kg) and Apgar score (appearance, pulse, grimace, activity and respiration), were compared among the 3 groups by student's t-test. **Results:** There was no significant difference in the gestational age (beta-thalassemia p=1.00 and iron-deficiency p=1.00), birth weight (beta-thalassemia p=0.078 and iron-deficiency p=1.00), and Apgar scores of all patients were higher than 7. **Conclusion:** This study indicated that pregnant women with beta-thalassemia or with iron-deficiency have no statistically significant effects on the maturation of babies when compared with the normal pregnancy group. The rationale behind awaits further investigation.

Key words: iron-deficiency, beta-thalassemia, haemoglobin pattern

Introduction

According to the WHO 2001, pregnancy with haemoglobin level below 11 g/dL was defined as anemia, which can cause by blood loss, haemolysis, iron deficiency and red cell production defect, such as bone marrow failure or thalassaemia. Haemoglobin is a protein to transport oxygen around each cell in the body and is composed of four polypeptide chains and an iron atom in the centre. In adult human, globin subunits of haemoglobin are composed of two alpha globins and two beta globins in each haemoglobin molecules, when the deficient synthesis of one or more of the globin will develop to thalassaemia. When iron-deficiency is occurred, the synthesis of haemoglobin structure also will be impaired.

Antenatal screening is an effective, fast, low cost and accurate genetic prenatal diagnosis in early gestation. Recent studies[1-3] have showed that severely anemia may increase the risk of low birth weight, preterm birth, and small in sizes for gestational age newborns. However, investigation of the beta-thalassaemia pregnancy outcomes is limited.[4] Therefore, it is a great interest to find out their relationship and the rationale behind. This is a retrospective study to investigate the relationship of birth weight, gestational age of birth in the first trimester in beta-thalassaemia and iron- deficiency pregnancies, and normal pregnancies with a background of haemoglobin (Hb) pattern, complete blood count (CBC), iron and ferritin. Our objective was to test the hypothesis that pregnancies outcomes in patients with beta-thalassaemia, or iron-deficiency are high risk pregnancies in Hong Kong private sector due to not enough oxygen supply for fetus.

Beta-thalassaemia

Thalassaemia is a common monogenetic disease worldwide and also common in Southern Asia. 8.3% Hong Kong populations have thalassaemia, especially beta-thalassaemia (3.4%).[5] Beta-thalassaemia has two genetic loci and located on chromosome 11 of the short arm. Point mutation in important functional sequences is commonly in beta-thalassaemia and more than 200 different beta-thalassaemia mutations can be searched in the Globin Gene Server (http://globin.cse.psu.edu/)[6] In Hong Kong Chinese people, the one of most common genetic mutation is deleted sequence in normal beta globin gene (Codon 41/42 [-CTTT] mutation).[7]

The mutation of beta-globin can be divided to two types, one is a complete absence of beta-globin chains (β^0) and the other one is reducing amount of beta-globin (β^+).

Beta-thalassaemia induces anemia due to reduction or absence of the beta globin chain synthesis, leading the excess alpha chains. Thus the hemoglobin production will be decreased in the red cells; reducing oxygen carriage to fetus is a main cause of fetal growth restriction. Beta-thalassaemia can be classified to minor (trait or carrier), intermedia and major sub-types, which depending on the degree of reducing of beta globin. In minor case, patients have one beta globin chain impaired (β^+/β) or absence (β^0/β). Their mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) are lower than normal, and the percentage of haemoglobin A2 is more than 3.5%. They are usually asymptomatic or sometimes have mild anemia. In major case, mutations of both beta-globin genes (e.g.β^+/β^+ orβ^+/β^0 orβ^0/β^0) can induce hypochromic microcytic anemia, bone marrow expansion, cardiac impairment, iron overload due to blood transfusion and gastro-intestinal iron absorption. They require life-long transfusion that also may develop complications relative to iron overload. Iron chelators therapy can help to prevent iron accumulation and other complications come from iron-related, such as liver cirrhosis, hepatocellular carcinoma, endocrinological and cardiac dysfunction, by binding to iron (as Fe^{3+}) with high affinity and is excreted as fecal iron and urinary iron. Splenectomy can be considered when increased the red cell consumption due to splenomegaly by the long term stimulation of anemia and hemolytic reactions. After splenectomy, transfusion requirement can be reduced. Bone marrow and cord blood transplantation is currently available approach to the treatment of beta-thalassaemia major, but the major limitation of allogeneic bone marrow transplantation is not easy to match a HLA identical donor. Bone marrow transplantation also has a risk, such as transmission of viral infections and chronic Graft-versus-host disease (GvHD). Gene therapy may be another approach to cure the thalassaemia by replacing the mutation genes or absence genes, but it also stays in experiment stage.[8] In intermedia case, their clinical status is in between minor and major, their beta-globin chains may have one or two alleles mutations (e.g.β^+/β^+), the production of beta-globin chains may have moderate impairment, sometimes they need a blood transfusion, but not regular.

Iron-deficiency

Iron-deficiency can be occurred when iron loss is incurred in iron absorption is impaired, imbalance in diet, blood loss or increasing requirement of iron such as pregnancy because maternal plasma volume and red cell mass are also increased for growing up to the fetus and placental vascularization at term[9], and a large amount of iron requirement during pregnancy. Severe iron-deficiency increases the risk of maternal death from anemic heart failure, pernatal infants loss, low birth weight and preterm birth.[10-11] Iron and folic acid supplement is a most common practice for prevention of iron deficiency anemia and contribute to a positive effect for preventing preterm birth and low birth weight.[12]

Materials and Methods

Sample collection

All patient data were collected from Shatin International Medical Centre Union Hospital, Shatin, Hong Kong SAR between January 2007 and December 2011 with the consent of the hospital in this study. This is a private hospital, all service need to charge by the patient. The blood sample collected by veinpuncture in a first trimester screening when the pregnant women attended. Women with singleton pregnancy included only and excluded prenatal death and perinatal death.

Sample size and data security

Antenatal screening blood tests included CBC, infection diseases and glucose level. When patient`s mean corpuscular volume (MCV) was lower than 80 fl or mean corpuscular hemoglobin (MCH) was lower than 27 pg, recommended to test a haemoglobin (Hb) pattern, iron level and ferritin with their husband, if couples suffer from alpha-thalassemia, the mutation genes may be inherited to the fetus, then it have a risk to develop alpha-thalassemia major or hydrops fetalis.[13] Within this period, 63 patients with beta-thalassaemia pregnancies, 26 patients with iron deficiency pregnancies (ferritin < 15 ug/L), and 83 normal pregnancies (normal CBC result without iron deficiency) were included. According to NHS confidentiality code of practice (2003) by Department of Health, United Kingdom, patient information provided in the this research will not be disclosed in a form that might identify a patient without his or her consent. Exclusion criteria were blood transfusion at least 3 months before first trimester screening in the study.

Inclusion

- Beta-thalassaemia pregnancy and normal pregnancy sample collected from 2007-2011 at the first trimester in Shatin Union Hospital.
- Beta-thalassaemia pregnancy diagnosis with MCH less than 27pg, MCV less than 80 fl, and elevated haemoglobin A2 3.5% or greater without iron deficiency.
- Iron deficiency
- Singleton pregnancy only

Exclusion

- Alpha-thalassaemia (Haemoglobin H present)
- Prenatal death or perinatal death.

Definition of clinically significant

Anemia was defined as haemoglobin less than 11 g/dL.[14] Beta-thalassaemia is characterised by a mean corpuscular volume (MCV) less than 80 fl or a mean corpuscular haemoglobin (MCH) less than 27 pg, and an elevated haemoglobin A2 by 3.5% or greater without iron deficiency.[15] Iron-deficiency was defined as ferritin level lower than 15 ug/L when measured in the absence of infection.[14] Low birth weight was defined as weight of baby less than 2500 g at birth. Babies were classified as preterm if the gestational age was less than 37 weeks. Fetal growth restriction was defined as the weight of a fetus is below the 10th percentile of its gestational age. The other variables included maternal age, maternal weight, glucose level, hepatitis B status, educations, parity, gravidity, newborn sex, smoking status, and alcoholic status.

Table 1: Summary of clinically significant in each test parameter

Pregnancy anemia	Hb concentration < 11 g/dL
Screening of beta-thalassemias	MCV< 80 fl, MCH< 27 pg and
Diagnosis of beta-thalassemias	Hb A2 > 3.5%
Iron-deficiency	Ferritin level < 15 ug/L
Low birth weight	< 2500 g
Preterm birth	< 37 weeks

Diagnosis tools

All patient samples were collected in Union Hospital and were analysed previously by PathLab Medical Laboratories Limited, Hong Kong. Haemoglobin electrophoresis is analyzed by BioRad VARIANT II system and complete blood count is analyzed by Bayer Diagnostics Advia 120/2120i Haematology System, Advia directly measuread Hb, MCV, red blood cell count (RBC), hematocrit (HCT), red blood cell distribution width (RDW) and hemoglobin content of reticulocytes (CHr), MCV was automatically calculated by dividing the total mass of hemoglobin by the number of red blood cells in a volume of blood. Ferritin was analyzed by chemiluminescence immunoassay (CLIA) analyzer, Abbott Architect i2000SR System with Ferritin Kit. Iron was analyzed by Ortho-Vitros Fusion System Fe Slide by spectrophotometry method.

Statistical analysis

All testing results were kept in the laboratory information system and only authorized person can access to the data. Student`s t-test is used to test differences in means, and X^2 test was employed to test differences in proportions. All statistical analyses are performed using SPSS 17.0 (SPSS Inx., Chicage, IL).

Result

Characteristics of pregnant women

There were 63 women in beta-thalassemias group, 26 women in iron-deficiency group and 83 women in the control group. Maternal ages, weight, parity, level of education were not significantly different in these 3 groups. Hb level was significantly lower in beta-thalassemias group and iron-deficiency group than in the control group. (9.88 g/dL; 10.2 g/dL and 12.1 g/dL; $p < 0.001$ and $p < 0.001$) (Table 2), p-value between beta-thalassemias group and iron-deficiency group is 0.472, but no significantly different in this 2 group.

Pregnancy outcome

Gestational age of birth was not significantly different in these 3 groups (β-thalassemias, p = 0.470; Iron deficiency, p =0.458). Birth weight was not significantly different in these 3 groups (β-thalassemias, p = 0.078; Iron deficiency, p =1.000). Cesarean delivery rate cannot be count in our study because the pregnancy women can choose the cesarean delivery to avoid the painful from labor. Apgar scores at 1 minute and 5 minutes more than 7 were not significantly different (β-thalassemias and Iron deficiency, p = 1.000) in 3 groups and no newborn have Apgar scores less than 7.

Table 2: Clinical Characteristics of Women with beta-thalassemias, iron-deficiency and controls*

Characteristics	Control group (n=83)	Beta (β) thalassemias group (n= 63)	p value	Iron Deficiency (n=26)	p value
Maternal age, y	30.9±4.36	30.9±5.07	1.000	30.4±5.29	1.000
Hb level, g/dL	12.1±0.94	9.88±0.92	<0.001	10.2±1.09	<0.001
Weight, Kg	68.9±9.19	66.7±7.57	0.354	67.7±8.50	1.000
Nulliparous	43 (51.8%)	25 (39.7%)	0.15	8 (30.8%)	0.61
Secondary Education or above	83 (100%)	61(96.8%)	0.233	26(100%)	1.000
Non-smoker	83 (100%)	62(98.4%)	0.645	26(100%)	1.000
Non-alcoholer	83 (100%)	63(100%)	1.000	26(100%)	1.000

*Value are given as mean±SD or number (percentage)

Table 3: Pregnancy outcome in beta-thalassemias, iron-deficiency and controls group*

Characteristics	Control group (n=83)	Beta (β) thalassemias group (n= 63)	p value	Iron Deficiency (n=26)	p value
Gestational age of birth, y	38.6±0.98	38.6±1.10	1.000	38.7±1.08	1.000
Birth Weigth, Kg	3.23±0.44	3.08±0.39	0.750	3.27±0.33	1.000
Apgar score 1min > 7	83 (100%)	63(100%)	1.000	26(100%)	1.000
Apgar score 5min > 7	83 (100%)	63(100%)	1.000	26(100%)	1.000

Discussion

Limitation of sample size

Thalassemia is a most common blood related genetic disorder in worldwide. In our study, we collected the haemoglobin pattern result of pregnancy women from 2007 to 2011 in first trimester to differentiate to 3 groups. In private sector, patients also want to get a good quality, faster, earlier and accurate service than public sector, thus they need to pay more money. Haemoglubin pattern is not a routine test, if the pregnancy woman MCV result is lower than 80 fL, we would suggest pregnancy women to screen the thalassemias to avoid a hydrops fetalis development. Some pregnancy women want to check haemoglobin pattern with normal CBC result due to her husband with anemia, thalassemias or unknown status. In previous study[16], CBC cannot screen out some atypical beta-thalassemia carriers which normal MCV and MCH, such as coinheritance heterozygous of beta-thalassemia with homozygous alpha^{+}-thalassemia or heterozygous alpha^{0}-thalassemia[17], thus haemoglubin pattern can cover the weak point of CBC. Some of pregnancies women check the antenatal test and haemoglobin pattern only, but labor in other hospital. It can explain that the limitation of sample size.

Analysis of population characteristics

From the medical record, most pregnancy women in Hong Kong private sectors are young middle age group; they also have good education and keep their health in good condition to maintain a good growing environment for their fetus. In local parent`s internet forum, they take some supplement, such as Maternal, Nestle. Therefore, nutrition and diet is enough in them. Otherwise, some low-income countries have not good facilities and condition for their beta-thalassemia pregnancy women, they occurred low birth weight and preterm labor.[4] Iron-deficiency pregnancy women can be found a preterm birth without iron treatment[12], but in our study, all iron-deficiency pregnancy have been treated. We found no statistically significant difference in low birth weight and preterm birth between thalassemia, iron-deficiency and control group.

In the study of northeast Thailand[18], thalassemia rather than iron-deficiency are major causes of pregnancy-related anemia. In our study, haemoglobin level is no significantly different in beta-thalassemia group and iron-deficiency group, but the mean of haemoglobin also show slightly low in beta-thalassemia group. It may be investigate more studies with a large sample size.

Study shortcoming

The major feeble of our study 1) small sample size has fewer representatives due to only one private hospital involved; 2) some pregnancies women may visit more than one doctor or more than one hospital, such as public hospital, the medical record has not a complete log in their treatment, such as number of transfusion and use of supplement; 3) We were not able to count the miscarriages, because we did not know the reason of pregnancy women no show after prenatal checkup.

Non-invasive prenatal diagnosis

Recent, the non-invasive prenatal diagnosis can be applicable for couples with beta-thalassemia. It can avoid the risks of the fetal miscarriage due to the invasive prenatal diagnosis. The detection of the absence of the paternal mutation in the maternal plasma can be excluded the mutant paternal allele has be inherited to the fetus. If the paternal mutation can be detected in maternal plasma, the fetus has a 50% chance to develop the beta-thalassemia major that depending on maternal mutation inherited or not. The invasive prenatal diagnosis procedures needed such as chorionic villus sampling and amniocentesis sampling.[19]

Conclusion

In conclusion, this study indicated that pregnant women with beta-thalassemia or with iron-deficiency have no statistically significant effects on the maturation of babies when compared with the normal pregnancy group. The rationale behind awaits further investigation.

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