

# Perinatal Outcomes among Thalassaemia Carriers in Hong Kong

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**Objective:** To compare adverse pregnancy outcomes, namely low birth weight, low Apgar scores at 1 and 5 minutes, extremely low Apgar scores at 1 and 5 minutes, and preterm delivery between thalassaemia carriers and healthy controls.

**Methods:** A retrospective review of all pregnancies delivered in a public hospital in Hong Kong in which routine thalassaemia screening was performed at the booking visit was conducted. The obstetric database and medical records from 1 July 2010 to 31 December 2011 were reviewed. Adverse obstetric outcomes between pregnant women who were thalassaemia carriers and healthy controls were compared. Outcomes of interest included low birth weight, low Apgar score at birth, and preterm delivery. Independent paired *t* test was used to analyse parametric data and Chi-square or Fisher's exact tests were used to analyse non-parametric data.

**Results:** A total of 7661 deliveries with valid data were identified during the study period, of which 287 (3.7%) occurred in thalassaemia carriers. Among the 287 thalassaemia carriers, 159 (55.4%), 107 (37.3%), and 21 (7.3%) were found to have  $\alpha$ ,  $\beta$ , and other haemoglobinopathy, respectively. Anaemia occurred in 6.2% (472/7620) of deliveries for which anaemia data were available. No significant differences in low birth weight ( $p=0.74$ ), low Apgar scores at 1 minute ( $p=0.66$ ) and 5 minutes ( $p=0.72$ ), or preterm delivery ( $p=0.83$ ) were noted between thalassaemia carriers and healthy controls. However, anaemia in pregnancy was significantly associated with adverse perinatal outcome, including low birth weight ( $p=0.03$ ), low Apgar scores at 1 minute ( $p=0.02$ ) and 5 minutes ( $p=0.04$ ), and preterm delivery ( $p=0.02$ ).

**Conclusion:** In general, the course of pregnancy of thalassaemia carriers was favourable without significant adverse perinatal outcomes. However, adverse outcomes were associated with anaemia. We recommend vigilant investigation, treatment, and prevention of anaemia to improve pregnancy outcomes.

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**Keywords:** Anemia; Apgar score; Infant, low birth weight; Pregnant women; Thalassaemia

## Introduction

Thalassaemia is a common hereditary disease in Hong Kong. The condition is characterised by impaired or abnormal production of  $\alpha$  or  $\beta$  globin chains. The prevalence and severity vary according to ethnicity, being high in Mediterranean regions and South-East Asia<sup>1-4</sup>.

In Hong Kong, thalassaemia is a highly prevalent disease. The prevalences of  $\alpha$ -thalassaemia and  $\beta$ -thalassaemia in the local population have been found to be 3-5% and 2.5-3.1%, respectively<sup>5-10</sup>. The rate for  $\alpha$ -thalassaemia carriers is estimated to be 4.3% and for  $\beta$ -thalassaemia carriers is 2.8%<sup>10</sup>.

Pregnant women with severe thalassaemia syndrome usually have anaemia with a haemoglobin (Hb) level of 70-100 g/L<sup>11,12</sup>. Physiological changes during pregnancy

will further increase the severity of anaemia in the mother, which could affect the pregnancy outcome as well as causing clinical symptoms<sup>13</sup>. These pregnancies may be associated with high rates of obstetric complications, especially intrauterine fetal growth restriction and preterm labour due to low Hb levels and fetal hypoxia during pregnancy<sup>1,14</sup>.

Several studies on the effects of thalassaemia trait on pregnancy outcomes have been conducted, but the results are inconsistent. While some studies<sup>1,15-18</sup> have shown favourable perinatal outcomes in patients with thalassaemia minor, other studies<sup>19-21</sup> have shown that

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thalassaemia is associated with an increased incidence of obstetric complications, particularly intrauterine fetal growth restriction and preterm labour. However, these studies were mostly conducted in Mediterranean countries and with small numbers of patients. Moreover, the study groups were often heterogeneous in nature, sometimes including patients with sickle cell trait<sup>16</sup>, which may not be applicable to the situation in Hong Kong. The need for more data, particularly for the local group of thalassaemia carriers in Hong Kong, was recognised.

The present study was designed to investigate the pregnancy outcomes of thalassaemia carriers in Hong Kong. During the 18-month period, a local group of thalassaemia carriers who delivered in a regional hospital in Hong Kong were examined. Queen Elizabeth Hospital (QEH), Hong Kong, is one of eight hospitals providing tertiary obstetrics and gynaecology services to the general population in Hong Kong. The hospital has an annual delivery rate of 6000 and it serves the entire obstetrics population in Kowloon Central district.

## Methods

A retrospective cohort study comparing the pregnancies of women with and without thalassaemia trait was performed. Deliveries from 1 July 2010 to 31 December 2011 at the QEH were included. The study was conducted with the approval of the Research Ethics Committee of QEH.

Thalassaemia screening in the Department of Obstetrics and Gynaecology was carried out according to the Hong Kong College of Obstetricians and Gynaecologists (HKCOG) guidelines<sup>22</sup>. Thalassaemia was diagnosed by universal antenatal blood test, which comprised complete blood count and mean corpuscular volume (MCV). The MCV cut-off for detecting thalassaemia carriers in this study was 80 fL according to a local study<sup>23</sup>.

In patients with MCV of <80 fL, maternal Hb pattern, maternal iron profile (including iron, total iron binding globulin, ferritin), and partner's MCV and Hb electrophoresis was checked. If the partner's MCV was normal ( $\geq 80$  fL), their fetus was regarded as not at risk of severe thalassaemia and no further fetal assessment was required<sup>24</sup>.

The detection of Hb H inclusion bodies was diagnostic for  $\alpha^0$ -thalassaemia.  $\beta$ -thalassaemia trait was diagnosed by an elevated Hb A<sub>2</sub> level ( $\geq 3.5\%$ ) and Hb F on high performance liquid chromatography<sup>24</sup>.

Iron deficiency can give rise to false-negative Hb H inclusion bodies and suppressed Hb A<sub>2</sub> levels. Therefore, a normal Hb pattern in the presence of iron deficiency anaemia cannot exclude underlying thalassaemia trait<sup>25</sup>. Patients with iron deficiency anaemia should therefore be treated with iron therapy first, followed by repeat MCV 4 weeks later before further investigations into their thalassaemia status.

If an individual is a carrier of both  $\alpha$ - and  $\beta$ -thalassaemia, especially in Chinese, Cypriot, and Sardinian ethnic groups<sup>26,27</sup>, Hb H inclusion bodies may be absent because both  $\alpha$  and  $\beta$  globin chain productions are reduced. Therefore, in the presence of a low MCV and normal iron status, a normal Hb pattern does not necessarily exclude  $\alpha$ -thalassaemia. A couple in this situation should be managed as having suspected  $\alpha$ -thalassaemia trait.

Couples with confirmed or suspected thalassaemia traits were referred to the Prenatal Diagnostic and Counselling Clinic for counselling. DNA analysis was performed at the Tsan Yuk Hospital laboratory.

For a couple with  $\alpha$ - or  $\beta$ -thalassaemia trait, their chance of having offspring with thalassaemia major is 1 in 4<sup>22</sup>. If the couple both had discordant thalassaemia traits, their fetus would not be at risk for serious thalassaemia unless one parent who carried  $\beta$ -thalassaemia trait had co-inheritance of  $\alpha$ -thalassaemia.

Couples were counselled on the inheritance risk to the fetus and different options of prenatal diagnosis. Chorionic villus sampling and amniocentesis were offered to all women at risk of carrying  $\beta$ -thalassaemia major fetuses. To women at risk of carrying homozygous  $\alpha^0$ -thalassaemia fetuses, the options of non-invasive serial ultrasonography examinations at 12, 18, and 30 weeks of gestation were offered as an alternative to invasive procedures in unaffected pregnancies<sup>24</sup>. Folic acid supplement would be given to pregnant thalassaemia carriers.

Gestational age was established in early gestation, either by clinical estimation using the last menstrual period (LMP) or by ultrasonography performed in the first trimester. In case of discrepancy between LMP and ultrasonography, the ultrasonography date was used.

Anaemia was defined as Hb level of <110 g/L in the first trimester and 105 g/L in the second trimester. This was according to the departmental protocol, which is in line with the current Centers for Disease Control guideline<sup>28</sup>.

The inclusion criteria for the study were women with low MCV (<80 fL), and who attended the antenatal clinic and delivered at the QEH. Women with unknown pregnancy outcomes were excluded. Data were retrieved from the computerised patient record database (Clinical Data Analysis and Recording System). The women's details had been entered into the electronic system by the midwives on admission to the antenatal ward.

Baseline demographics, including ethnicity, maternal age, parity, multiple pregnancy, and use of fertility treatments were compared. Perinatal outcomes, including low birth weight (defined as body weight <2500 g), low Apgar scores at 1 and 5 minutes (defined as <7), extremely low Apgar scores at 1 and 5 minutes (defined as <3), and preterm delivery (defined as delivery <37 weeks), were compared.

For statistical analysis, independent paired *t* test was used to analyse parametric data and Chi-square or Fisher's exact tests was used to analyse non-parametric data. Statistical analysis was performed by using the Statistical Package for the Social Sciences, Windows SPSS version 17.0 (SPSS Inc., Chicago [IL], US). Descriptive data were presented as percentages. A value of  $p < 0.05$  was considered statistically significant. Assuming the prevalence of thalassaemia carriers in local population was around 8%,

**Table 1. Prevalence of thalassaemia carrier status, suspected  $\alpha$ -thalassaemia, and iron deficiency anaemia among pregnant women in Hong Kong (n=7661)**

Condition	No. (%)
Healthy population	6659 (86.9)
Thalassaemia carriers	287 (3.7)
Suspected $\alpha$ -thalassaemia carriers	370 (4.8)
Low mean corpuscular volume (non-specific)	304 (4.0)
Iron deficiency anaemia	41 (0.5)

an allocation ratio ( $\phi$ ) of 11.5 ( $[(100-8)/8]$ ) was derived. For a significance level  $\alpha$  of 0.05 (2-sided), statistical power 80%, and allocation ratio of 11.5, the study sample required for thalassaemia trait would be 497 and the total sample size required was 6213.

## Results

From 1 July 2010 to 31 December, 2011, 9622 cases were identified, of which 7661 (79.6%) deliveries were identified to have complete data. Data were incomplete because some pregnant women who delivered at the QEH did not attend or defaulted antenatal care. Of the 7661 deliveries, 287 (3.7%) pregnancies occurred in thalassaemia carriers. Table 1 summarises the percentages of healthy controls, thalassaemia carriers, suspected  $\alpha$ -thalassaemia carriers, low MCV of unknown cause, and iron deficiency anaemia in the study population. Among the 287 thalassaemia carriers, 159 (55.4%), 107 (37.3%), and 21 (7.3%) were found to have  $\alpha$ ,  $\beta$ , and other haemoglobinopathy, respectively.

The women's clinical characteristics, including ethnicity, maternal age, parity, multiple pregnancy, and use of fertility treatments were compared (Table 2). The demographic data were incomplete for age, in-vitro fertilisation, and race in 1672 (24%) cases due to problems in data entry and data retrieval from the computerised database (Table 3). Thalassaemia was statistically more common in pregnancies in women of >35 years ( $p=0.005$ ) and in women of Chinese ethnicity ( $p < 0.001$ ).

Table 4 summarises the pregnancy outcomes between thalassaemia carriers and healthy controls. Thalassaemia trait was not significantly associated with adverse pregnancy outcomes, including low birth weight ( $p=0.74$ ), low Apgar scores at 1 minute ( $p=0.66$ ) and 5 minutes ( $p=0.72$ ), extremely low Apgar scores at 1 minute ( $p=0.72$ ) and 5 minutes ( $p=0.62$ ), and preterm delivery ( $p=0.83$ ).

**Table 2. Demographic characteristics of thalassaemia carriers compared with healthy controls**

Item	No. (%)		p Value (Chi-square test)
	Thalassaemia carriers (n=287)	Healthy controls (n=6659)	
Parity			<0.091
0	172 (59.9)	3503 (52.6)	
1	92 (32.1)	2590 (38.9)	
2-4	23 (8.0)	559 (8.4)	
$\geq 5$	0	7 (0.1)	
Twins	6 (2.1)	145 (2.2)	0.49

Adverse pregnancy outcomes in patients with and without anaemia were compared. Data for anaemia were available for 7620 (99.5%) of 7661 patients. Anaemia occurred in 472 (6.2%) of the study population, which included those with thalassaemia and other causes of anaemia.

The pregnancy outcomes for women with anaemia and healthy controls are shown in Table 5. Anaemia in pregnancy was significantly associated with low birth weight ( $p=0.03$ ), low Apgar scores at 1 minute ( $p=0.02$ ) and 5 minutes ( $p=0.04$ ), as well as preterm delivery ( $p=0.02$ ).

Table 6 summaries the pregnancy outcomes in

thalassaemia carriers with or without anaemia. There was a trend towards low birth weight, low Apgar scores at 1 minute and 5 minutes, extremely low Apgar score at 1 minute, and preterm labour for thalassaemia carriers with anaemia (Table 6). However, as the absolute numbers of the cases were small, these outcomes did not reach statistical significance.

Similarly, subgroup analyses of pregnancy outcomes for women with  $\alpha$ -thalassaemia or  $\beta$ -thalassaemia with or without anaemia were done. For  $\alpha$ -thalassaemia, there were trends towards low birth weight (8.7% vs. 5.9%), extremely low Apgar score at 1 minute (4.3% vs. 0.7%), and preterm labour (4.3% vs. 1.5%) in the group with

**Table 3. Baseline demographic characteristics of thalassaemia carriers compared with healthy controls**

Item	No. (%)		p Value (Chi-square test)
	Thalassaemia carriers (n=130*)	Healthy controls (n=5144*)	
Age >35 years	23 (17.6)	1580 (30.7)	0.005
In-vitro fertilisation	2 (1.5)	73 (1.4)	0.437
Chinese ethnicity	124 (95.4)	4744 (92.2)	<0.001

\* Data were missing in 157 thalassaemia carriers and 1515 healthy controls

**Table 4. Pregnancy outcomes for thalassaemia carriers compared with healthy controls**

Item	No. (%)		p Value (Chi-square test)
	Thalassaemia carriers (n=287)	Healthy controls (n=6659)	
Low birth weight (<2500 g)	20 (7.0)	432 (6.5)	0.74
Low Apgar score at 1 minute	12 (4.2)	246 (3.7)	0.66
Low Apgar score at 5 minutes	2 (0.7)	45 (0.7)	0.72*
Extremely low Apgar score at 1 minute	2 (0.7)	45 (0.7)	0.72*
Extremely low Apgar score at 5 minutes	0	24 (0.4)	0.62*
Preterm delivery	6 (2.1)	128 (1.9)	0.83*

\* Fisher's exact test

**Table 5. Adverse pregnancy outcomes in anaemia patients and healthy controls**

Item	No. (%)		p Value (Chi-square test)
	Anaemia (n=472)	Healthy controls (n = 7148)	
Low birth weight (<2500 g)	43 (9.1)	473 (6.6)	0.03
Low Apgar score at 1 minute (<7)	27 (5.7)	263 (3.7)	0.02
Low Apgar score at 5 minutes (<7)	7 (1.5)	46 (0.6)	0.04*
Extremely low Apgar score at 1 minute (<3)	6 (1.3)	45 (0.6)	0.13*
Extremely low Apgar score at 5 minutes (<3)	4 (0.8)	23 (0.3)	0.08*
Preterm delivery	16 (3.4)	136 (1.9)	0.02

\* Fisher's exact test

**Table 6. Pregnancy outcomes in anaemic and non-anaemic thalassaemia trait patients**

Item	No. (%) of thalassaemia carriers		p Value (Chi-square test)*
	With anaemia (n=81)	Without anaemia (n=206)	
Low birth weight (<2500 g)	6 (7.4)	14 (6.8)	0.85
Low Apgar score at 1 minute (<7)	5 (6.2)	7 (3.4)	0.33
Low Apgar score at 5 minutes (<7)	0	2 (1.0)	1
Extremely low Apgar score at 1 minute	1 (1.2)	1 (0.5)	0.48
Preterm delivery	4 (4.9)	2 (1.0)	0.05

\* Fisher's exact test

anaemia, but these did not reach statistical significance ( $p=0.63$ ,  $p=0.26$ ,  $p=0.37$ , respectively). The results were similar in the women with  $\beta$ -thalassaemia, with trends towards low birth weight (7.7% vs. 5.5%), low Apgar score at 1 minute (7.7% vs. 0%), and preterm delivery (5.8% vs. 0%). As the absolute numbers were small, these outcomes also did not reach statistical significance ( $p=0.71$ ,  $p=0.05$ ,  $p=0.11$ , respectively).

## Discussion

The design of this study differed from most other studies investigating pregnancy outcomes in thalassaemia carriers. Most published studies were performed in Mediterranean countries such as Israel or Greece, and focused on  $\beta$ -thalassaemia minor and pregnancy outcomes. To the authors' knowledge, this is the first published study to investigate perinatal outcomes of  $\alpha$ -,  $\beta$ -, and other thalassaemia carriers in Hong Kong. Universal screening was intended to identify all thalassaemia carriers among the pregnant women to provide the most comprehensive and representative population.

This study has shown that pregnancy outcomes for thalassaemia carriers were favourable. In this series of 287 thalassaemia carriers, there was no association with adverse pregnancy outcomes. Low birth weight, low Apgar score at birth, extremely low Apgar score, and preterm labour are comparable between thalassaemia carriers and the healthy population. These findings are consistent with those reported by Sheiner et al<sup>15</sup> who reported favourable perinatal outcome in patients with thalassaemia minor.

Some studies have shown that thalassaemia was associated with an increased incidence of obstetric complications. Studies<sup>19-21</sup> have shown increased rates of fetal growth restriction, preterm birth, and low birth weight in thalassaemia carriers despite attempts to maintain their Hb levels of >70 g/L. Unlike our study, one Thai

study<sup>20</sup> had a higher proportion of Hb E trait (12% of the population with thalassaemia trait), and  $\alpha$ -thalassaemia and  $\beta$ -thalassaemia accounted for 6.6% and 3.7% of this population, respectively, which may account for the differences in the study outcomes.

In this study, the prevalence of anaemia was 6.2%, which was higher than the proportion quoted in another local study<sup>29</sup>. The reason for the difference may be the different cut-off value used for anaemia (100 g/L vs. 110 g/L in this study). Another reason may be an influx of Chinese immigrants who have not had adequate antenatal care or optimisation of Hb before delivery, leading to an increased prevalence of anaemia in pregnancy.

This study has shown that anaemia was significantly associated with adverse pregnancy outcomes. Low birth weight, low Apgar scores at 1 minute and 5 minutes, and preterm labour were significantly associated with anaemia in pregnancy. It is possible that chronic maternal anaemia during gestation might lead to fetal hypoxia<sup>1,14</sup>. Thus, it was suggested that Hb concentration should be maintained above 100 g/L during pregnancy to optimise pregnancy outcomes<sup>30,31</sup>.

In thalassaemia carriers, anaemia is common, with an Hb level of 10-20 g/L lower than in a healthy person of the same age and sex<sup>32,33</sup>. Patients with anaemia are usually asymptomatic except during times of stress such as pregnancy<sup>34</sup>. In pregnancy, anaemia is further aggravated by physiological changes. Pregnant women who are thalassaemia carriers often have a lower Hb level of 70-100 g/L, and variable degrees of splenomegaly<sup>11,12</sup>. In severe cases, blood transfusions are sometimes necessary. In thalassaemia carriers, maternal anaemia superimposed on thalassaemia carrier state might worsen fetal hypoxia, which may predispose the fetus to distress during and after the delivery process. Therefore, some authors<sup>30,31</sup>

have advocated maintaining the Hb level of >100 g/L to minimise the effect of chronic anaemia on the fetus.

It was recommended by the HKCOG guidelines<sup>22</sup> that universal screening for thalassaemia carrier status using MCV/mean corpuscular Hb be carried out at booking visits, so that at-risk couples could be offered genetic counselling. At the QEH, routine screening for MCV and further investigation for low MCV was performed in all patients during the booking antenatal visit. Couples with confirmed or suspected thalassaemia traits were referred to the Prenatal Diagnostic and Counselling Clinic for counselling and DNA analysis performed to confirm suspected cases. The availability of the database in the Department of Obstetrics and Gynaecology enables study of adverse outcomes between patients with thalassaemia and healthy controls.

In this study, the prevalence of confirmed thalassaemia in the population was 3.8%, which was lower than the proportion quoted in other studies<sup>10,35</sup>. One of the possibilities was that patients who were suspected  $\alpha$ -thalassaemia carriers (4.8%) were not fully investigated with molecular studies. For genetic counselling, further investigation for these patients with suspected thalassaemia trait was deemed unnecessary if their partner's MCV was normal. Another possibility was that 4.0% of patients had undefined low MCV. This group might have included patients with  $\alpha$ - or  $\beta$ -thalassaemia trait. Unfortunately, further investigations, such as molecular studies, were not done. If molecular analysis had been performed, the estimated rate of thalassaemia carriers would have been increased to approximately 7-8%, which would be closer to the prevalence quoted in previous studies<sup>10,35</sup>. Therefore, one of the limitations of this study was the underestimation of thalassaemia carriers in the results.

The weakness of this study was that it was retrospective, with data retrieved from the hospital electronic database. There might have been incomplete data collection or incorrect entry of data or coding. Thalassaemia status was unknown for some women for

the following reasons: (1) pregnant women who delivered in the QEH defaulted antenatal care and investigations; (2) mothers from mainland China attended one or two antenatal sessions just prior to delivery without adequate investigation for low MCV status; (3) some mothers did not have antenatal care in Hong Kong and came to the hospital for delivery only; and (4) pregnant women with low MCV, whose partner's MCV was normal, did not have further investigation using DNA study. Thus, some women with thalassaemia trait might have been missed.

Other factors accountable for adverse pregnancy outcomes such as chronic maternal illness, socio-economic factors, poor antenatal attendance, and lack of proper surveillance in late pregnancy were not taken into account.

This study has shown that anaemia in pregnancy was found to be significantly associated with adverse pregnancy outcomes, including low birth weight, low Apgar scores, and preterm labour (Table 5). Therefore, optimisation of Hb levels should be promoted. Ideally, this approach should start preconceptually with health education, premarital check, and preconceptual folic acid supplement, which can prevent anaemia as well as reduce the risk of neural tube defects. Any underlying causes of anaemia should be investigated and treated early. In patients with iron deficiency, use of appropriate supplements should be recommended. Serial growth assessment should be performed for high-risk patients to identify problems for early intervention. Growth assessment should include third-trimester ultrasonography for fetal weight. Further prospective studies of patients with thalassaemia trait should investigate the efficacy of folic acid in correcting anaemia and efficacy of growth assessment by ultrasonography in the third trimester.

In conclusion, the course of pregnancy of thalassaemia carriers was favourable without significant adverse perinatal outcomes. However, adverse outcomes were associated with anaemia. Vigilant investigation, treatment, and prevention of anaemia to improve pregnancy outcomes are recommended.

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