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α-Thalassaemia trait and gestational diabetes mellitus in Hong Kong

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Abstract

Aims/hypothesis. The purpose of this study was to examine the association between maternal α-thalassaemia trait and the occurrence of gestational diabetes mellitus in at-risk Chinese women in Hong Kong.
Methods. From 3320 pregnant women who had delivered in our hospital and undergone the oral glucose tolerance test for various risk factors over a three-year period, 163 with α-thalassaemia trait were identified (study group). The control group consisted of 163 women chosen from the next patient that was matched for maternal age and parity, following each index case. Comparison was made in the incidence of gestational diabetes mellitus defined by the World Health Organisation criteria, obstetric complications, and perinatal outcome.
Results. The incidence of gestational diabetes mellitus was higher in the study group (62.0 % vs 14.7 %, $p < 0.0001$) which had a higher pre-pregnancy body mass index and lower haemoglobin concentrations. Although more patients in the study group had risk factors (41.7 % vs 26.4 %, $p = 0.003$), there was no difference in the pregnancy outcome or perinatal complications. Among the gestational diabetic women, those with α-thalassaemia trait were considerably younger and their infants had lower body mass index but there was no significant difference in the outcome. On multiple logistic regression analysis, the α-thalassaemia trait remained an important factor in the diagnosis of gestational diabetes (OR 11.74, 95 % CI 6.37–21.63).
Conclusion/interpretation. Among women at risk of gestational diabetes, the presence of the α-thalassaemia trait is an additional risk factor for gestational diabetes mellitus. [Diabetologia (2001) 44: 966–971]

Keywords Gestational diabetes mellitus, α-thalassaemia trait, pregnancy outcome.

It is well documented that the health of subjects with β-thalassaemia major or intermedia is complicated by an increased risk of diabetes mellitus and other endocrine disorders [1–7]. This is consequent to haemosiderosis, which is due to repeated blood transfusion and chronic haemolysis. However, little is known about the risk of diabetes mellitus, whether as a complication of treatment or of the underlying condition, in subjects with α-thalassaemia.

Alpha-thalassaemia is absent or rare in Europe and Northern Asia and China [8, 9]. In Southern China and Southeast Asia, the α-thalassaemia trait, haemoglobin H disease, and α- thalassaemia hydrops fetalis are found [8]. The incidence of the α-thalassaemia trait is about 6 % around Hong Kong [10, 11], and up to 15 % in Southern China [9]. A recent study [12] confirmed that 5 % of the Chinese population in Hong Kong carry the α-thalassaemia trait. The overwhelming majority (4.5 %) are carriers of the Southeast Asian type of deletion, in which both α-globin genes on the same chromosome 16 are deleted (α-1

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Abbreviations: GDM, gestational diabetes mellitus; MCV, mean cell volume; WHO, World Health Organisation; LGA, large-for-gestational age; OR odds ratio

thalassaemia), while $\alpha^{3,7}$ and $\alpha^{4,2}$ deletion were found in 0.3 % and 0.2 % respectively. As the perinatal mortality of infants with homozygous α-1/α-1 thalassaemia (haemoglobin Bart's hydrops fetalis syndrome) is 100 % [8, 12, 13], pregnancy was often discouraged in couples of which both were carriers of the α-thalassaemia trait in the past. With the advent of prenatal diagnosis, it is now possible to confirm or exclude homozygous α-thalassaemia in the fetus [14]. Thus more women with α-thalassaemia trait can continue with their pregnancies, and this has probably accounted for the increase in the incidence of the α-thalassaemia trait in our parturients from 1.7 % in 1988 to 3.2 % in 1998 (data from our annual statistics).

In a study on the relation between maternal anaemia and pregnancy outcome in Hong Kong, it was found that the incidence of gestational diabetes mellitus (GDM) was double among women with anaemia due to the thalassaemia trait compared to women with anaemia due to iron deficiency [15]. Although the majority of the women with the thalassaemia trait had the α-thalassaemia trait, the increasing incidence of this group of parturients could not explain the significantly higher prevalence of GDM compared with parturients with iron deficiency anaemia in our population, unless the α-thalassaemia trait could be a predisposing factor to GDM. In view of a recent case report of Type I (insulin-dependent) diabetes mellitus in a 37-year-old man with haemoglobin H disease [16], we suspect that the presence of α-thalassaemia trait could be associated with the development of GDM. In order to examine this hypothesis, we have carried out a retrospective case-control study over a 3-year period on the obstetric patients at risk of developing GDM who delivered in our hospital.

Subjects and methods

Our hospital is a regional hospital that caters to public patients only, with about 5000 deliveries a year and the majority of our patients (> 95 %) are ethnic Chinese. In Hong Kong, the standard practice is to routinely check the haemoglobin (Hb) concentration, mean corpuscular volume (MCV) and blood group of patients routinely at their first antenatal visit. The MCV screening is done to identify mothers at risk of carrying the thalassaemia traits [12]. Those with a MCV of less than 80 fl will be investigated further with Hb electrophoresis and examination of the blood smear for Haemoglobin-H inclusion bodies, and iron status (serum ferritin measurement) will be determined if the Hb concentration is less than 10 g/dl. The partner also undergoes the MCV screening. If both partners have low MCV, prenatal diagnosis is done to determine if the fetus is affected by homozygous α-thalassaemia, for which termination of pregnancy would be offered. The diagnosis of α-thalassaemia trait is based on the finding of normal or decreased percentage of haemoglobin A_2 and the presence of Haemoglobin-H inclusion bodies. Conducting studies on the genotype of α-thalassaemia carriers is not a routine procedure of the clinical service, since it is known from previous studies that the great majority of the carriers have the α-1 thalassaemia trait.

A multivitamin preparation containing 29 mg of elemental iron is prescribed to all patients from 20 weeks of gestation. Folic acid 5 mg daily is prescribed to women diagnosed to have the α-thalassaemia trait irrespective of their Hb content, but iron therapy is not given unless concomitant iron deficiency, which is very uncommon in this group of women, is diagnosed at the initial screening. Otherwise the pregnancy is managed in a manner similar to that for the non-anaemic women. At 28 to 30 weeks Hb is estimated again to identify mothers who might have developed anaemia and further therapy will be given as necessary. Blood transfusion however is not given before delivery unless the Hb is less than 8 g/dl and the women are symptomatic but blood will be cross-matched and reserved during labour and delivery for transfusion where indicated.

Our hospital adopts a universal screening programme for GDM by means of risk factors and random glucose at the third trimester. Women with risk factors for developing GDM, such as advanced maternal age (> 35 years), relevant past obstetric and family history, pre-pregnant weight of 75 kg or more, and recurrent and/or significant glycosuria, or other findings such as polyhydramnios or excessive fetal growth during the index pregnancy, take the 75 g OGTT and the result is interpreted by the World Health Organisation criteria [17]. In addition, all women at low risk and those with previous normal OGTT have blood drawn for random blood glucose testing at the beginning of the third trimester (28–30 weeks). A positive screen refers to a glucose concentration of more than 5.8 mmol/l if less than 2 h postprandial, and more than 5.0 mmol/l if more than 2 h postprandial; these patients also undergo the 75 g OGTT. Women diagnosed to have GDM are referred to a dietitian and their diet controlled (30 kcal/kg). Then they are assessed with a 2-h postprandial blood sugar profile. Insulin therapy is given for inadequate control (postprandial glucose > 7 mmol/l) if dietary readjustment failed to normalize the blood sugar profile. The diagnosis and management of GDM in our population has been described [18].

From a database on women who had undergone the OGTT from 1994 to 1996, women who were carriers of the α-thalassaemia trait and delivered in our hospital were identified. From amongst the other women without haemoglobinopathies, those closest to each index case and matched for exact age and parity, and ethnicity, were selected as controls in order to minimise the effect of confounding factors in maternal demographics. We matched for parity because parity affects pregnancy outcome and is an important risk factor for GDM in Asian women [19]. We have not matched for other risk factors such as family history or obesity because of the relatively low incidence of these factors. Maternal demographics, OGTT and Hb results, pregnancy complications and infant outcome were compared between the groups with and without the α-thalassaemia trait. The pregnancy complications we examined included caesarean section [20–22], pre-eclampsia [20–22], antepartum haemorrhage [22], and preterm birth [21]. For infant outcome, large-for-gestational age (LGA) is defined as birthweight above the 90th percentile for gestational age in our local population according to our standardised chart. Statistical analysis was done with the Student's *t* test, chi square or Fisher's exact test depending on the size of each cell and the odds ratio was calculated where indicated, using a commercial statistical package (Statistical Package for Social Sciences).

Results

During the study, there were 14 450 deliveries and the overall incidence of GDM was 12.1 %. Of the 3320

Table 1. Maternal and infant demographic data in study and control groups

	Study group (n = 163)	Control group (n = 163)	Difference
Age (years)	30.8 ± 4.5	30.8 ± 4.5	NS
Weight (kg)			
booking	53.9 ± 8.6	52.6 ± 7.3	NS
pre-delivery	65.6 ± 8.7	65.1 ± 7.9	NS
Height (cm)	154.7 ± 5.7	155.4 ± 5.5	NS
BMI (kg/M^2)			
booking	22.6 ± 3.4	21.8 ± 3.1	p = 0.038
pre-delivery	27.4 ± 3.3	27.0 ± 3.2	NS
Hb (g/dl)			
booking	11.2 ± 1.1	12.4 ± 1.0	p = 0.000
third trimester	10.7 ± 1.0	11.7 ± 0.9	p = 0.000
OGTT (mmol/l)			
0-h	4.6 ± 0.5	4.4 ± 0.4	p = 0.014
2-h	8.0 ± 1.7	6.7 ± 1.3	p = 0.000
Gestation at OGTT (weeks)			
Diagnosis			
IGT (%) *	96 (58.9)	24 (14.7)	p = 0.000
GDM (%)	5 (3.1)	0	
Gestation (weeks)	38.9 ± 1.5	39.0 ± 1.6	NS
Birthweight (g)	3190 ± 497	3198 ± 422	NS
Crown Heel Length (cm)	50.0 ± 2.1	50.3 ± 2.1	NS
Apgar Score at 1 min	8.8 ± 1.2	8.6 ± 1.3	NS
5 min	9.8 ± 05	9.8 ± 0.5	NS

Comparison with the Student's t test or * chi square test as indicated

Table 2. Risk factors for GDM in the study and control groups

	Study group (n = 163)	Control group (n = 163)	chi square test
Presence of risk factors	67 (41.1)	43 (26.4)	p = 0.003
Family history	23 (14.1)	16 (9.8)	NS
Advanced age	34 (20.9)	34 (20.9)	NS
Past history	10 (6.1)	4 (2.5)	NS
Obesity	4 (8.6)	1 (6.1)	NS
Glycosuria	5 (3.1)	1 (0.6)	NS
Other	3 (1.8)	2 (1.3)	NS
Combination	1 (0.6)	0	NS

Results expressed in number (% of whole group)

Table 3. Pregnancy complications and outcome in study and control groups

	Study group (n = 163)	Control group (n = 163)	chi square test
Preterm labour	3.7	3.1	NS
Prelabour rupture of membranes	16.0	14.7	NS
Antepartum haemorrhage	12.3	5.5	p = 0.031
Pre-eclampsia	5.5	4.3	NS
Induced labour	16.0	18.4	NS
Delivery before onset of labour	7.4	6.7	NS
Instrumental delivery	21.6	23.9	NS
Caesarean section	16.0	17.8	NS

Results expressed in %

patients in the database, α-thalassaemia trait was diagnosed in 163 Chinese patients (4.9%). The mean maternal age was 30.8 ± 4.5 years, and the incidence of nulliparous women was 49.7% (81/163). There was no difference in the maternal pre-pregnancy or pre-delivery weight, height, or pre-delivery BMI between the study and control groups, but pre-pregnancy BMI was significantly higher in the study group (Table 1). As expected, the Hb concentrations at booking and the third trimester were higher in the control group but the results of the OGTT were higher in the study group. This was due to the fact that 62.0% of the study group had glucose intolerance, in contrast to the 14.7% in the control group (p = 0.000, OR 9.44, 95% CI 5.52–16.13). The incidence of GDM in the non-thalassaemic group was 21.9%. While all the patients with glucose intolerance in the control group belonged to the WHO category of impaired glucose tolerance (IGT), 3.1% in the study group had diabetes mellitus, and the ratio of IGT to diabetes mellitus was 19:1. However, there was no difference in the gestatrional age, the size of the newborn, or Apgar scores. All the patients with gestational diabetes mellitus in the study and control groups were managed successfully with diet treatment.

Table 4. Perinatal outcome in study and controls groups

	Study group (n = 163)	Control group (n = 163)	chi square test
Macrosomia (≥ 4000 g)	4.3	3.1	NS
Large-for-gestational age	13.6	11.7	NS
Apgar score < 7			
1 min	4.5	8.0	NS
5 min	0	0	NS
Phototherapy for jaundice	14.2	9.2	NS
Meconium aspiration syndrome	0.6	0.6	NS
Clinical sepsis	4.3	4.9	NS
Neurological complications	0.6	0.6	NS
Metabolic complications	2.0	2.0	NS
Birth trauma	1.3	1.3	NS

Results expressed in %

The indications for OGTT were examined in Table 2. Risk factors were found to be present in 41.7 % of the study group and 26.4 % of the controls (p = 0.003, OR 2.02, 95 % CI 1.27–3.22) and often more than one risk factor could be found with the same case. However, there was no difference in the pattern or distribution of the risk factors. Although the incidence of diabetes mellitus in the first-degree relatives was higher in the study group, the difference was not statistically significant. Despite the higher incidence of GDM in the study group, there was no difference in the incidence of the common obstetric complications except for a higher incidence of antepartum haemorrhage in the study group (p = 0.031, OR 2.41, 95 % CI 1.06–5.47, Table 3). There was also no difference in the type of labour or the mode of delivery. Similarly, there was no difference in the perinatal outcome (Table 4).

The GDM pregnancies were further analysed according to the presence or absence of the maternal α-thalassaemia trait. Except for a younger maternal age and a lower infant BMI in the study group, there was no difference in the maternal or newborn characteristics, or in the mean values of the antepartum and postnatal OGTT (Table 5). There was no difference in the incidence of the common obstetric and perinatal complications between these two groups (Table 6).

To determine the role of maternal α-thalassaemia trait in the development of GDM, stepwise multiple logistic regression analysis was carried out. The risk factors analysed included high BMI (> 26 kg/m^2) before pregnancy, advanced maternal age (≥ 35 years), family history of diabetes in first degree relatives, past history of GDM, and the presence of α-thalassaemia trait. The presence of α-thalassaemia trait was the most significant factor (OR 11.74, 95 % CI 6.37–21.63), followed by past history of GDM (OR 9.57, 95 % CI 1.98–46.14), advanced maternal age (OR 5.29, 95 % CI 2.56–10.93), and high pre-pregnancy BMI (OR 2.61, 95 % CI 1.08–6.32). Family history was excluded as a significant factor (OR 2.26, 95 % CI 0.95–5.36).

Table 5. Comparison between GDM women with and without the α-thalassaemia trait

	With thalassaemia (n = 101)	Without thalassaemia (n = 24)	Difference
Age (years)	31.5 ± 4.4	34.5 ± 4.7	p = 0.004
Weight (kg)			
booking	55.0 ± 9.5	54.8 ± 7.0	NS
pre-delivery	65.8 ± 9.4	65.5 ± 7.1	NS
Height (cm)	154.8 ± 5.5	153.9 ± 4.1	NS
BMI (kg/M^2)			
booking	23.0 ± 3.8	23.2 ± 3.3	NS
pre-delivery	27.5 ± 3.6	27.7 ± 3.5	NS
Hb (g/dL)			
booking	11.3 ± 1.1	12.5 ± 0.9	p = 0.000
third trimester	10.7 ± 1.0	11.8 ± 0.8	p = 0.000
OGTT (mmol/l)			
0 h	4.6 ± 0.5	4.6 ± 0.5	NS
2 h	9.0 ± 0.9	8.9 ± 0.8	NS
Gestation (weeks)	38.8 ± 1.4	39.2 ± 1.3	NS
Birthweight (g)	3197 ± 466	3301 ± 438	NS
Crown-heel length (cm)	50.2 ± 2.2	50.1 ± 1.8	NS
Infant BMI (kg/M^2)	12.7 ± 1.2	13.3 ± 1.5	p = 0.049
Placental Weight	616 ± 134	641 ± 115	NS
Postnatal OGTT			
0 h	5.0 ± 0.5	5.0 ± 0.3	NS
2 h	6.3 ± 1.7	6.0 ± 1.3	NS

Comparison with the Student's t test

Table 6. Pregnancy outcome and postnatal glucose tolerance status in GDM women with and without the thalasaemia trait

	With thalassaemia (n = 101)	Without thalassaemia (n = 24)	chi square test
Nulliparous women	49.5	41.7	NS
Maternal age ≥ 35 years	25.7	50.0	p = 0.020
Preterm labour	3.0	0	NS
Prelabour rupture of membranes	15.0	8.3	NS
Antepartum haemorrhage	15.0	16.7	NS
Group B Streptococcus carriage	3.1	0	NS
Pre-eclampsia	8.9	8.3	NS
Caesarean section	17.0	20.8	NS
Infant macrosomia	5.0	8.3	NS
Large for gestational age	17.0	12.5	NS
Phototherapy for jaundice	16.7	29.2	NS
Clinical sepsis	5.0	4.2	NS
Metabolic complications	1.0	4.2	NS
Postnatal OGTT	80.2 (81/101)	70.8 (17/24)	
Abnormal results	18.5 (15/81)	17.6 (3/17)	NS
IGT	17.3 (14/81)	17.6 (3/17)	
Diabetes mellitus	1.2 (1/81)	0	

Results expressed in % and compared with the chi square test

Discussion

In this study, the prevalence of GDM in women with α-thalassemia trait was 62%, a figure that was four-fold higher than the control subjects who were also at risk but without the α- thalassaemia trait. It was possible that the higher prevalence of GDM in the women with the α-thalassemia trait was related to risk factors such as age, parity, and maternal BMI, all of which have been shown to be higher in the women with GDM in our population [18]. While the pre-pregnancy BMI was higher in the study group, the difference was clinically small. In addition, although the overall incidence of risk factors was increased in the women with the α-thalassaemia trait, there was no difference in the incidence of the individual factors or in the distribution of these factors. Multiple logistic regression analysis confirmed that the presence of α-thalassaemia trait was the most significant risk factor.

The underlying cause of the association between α-thalassaemia trait and GDM is not known. There is a relation between iron overload and the development of diabetes mellitus, such as in the patients with transfusion-treated β-thalassaemia major [1] and genetic haemochromatosis [23]. Increased iron store in the women with α-thalassaemia trait could be a contributing factor. This is because the anaemia found in the pregnant women with α-thalassemia trait is due to the defect in globin chain synthesis and their iron stores tend to be normal or high, dependent on actual iron utilisation [15]. However, a high serum ferritin concentration is usually associated with Hb H disease and not with the α-1 thalassemia trait, and blood transfusion to maintain the Hb concentration is not necessary for these women. Also there is no known association between the α-thalassaemia trait and haemochromatosis. Although maternal third trimester serum ferritin concentration has been shown to be significantly higher in non-anaemic non-thalassaemic women with IGT compared with non-diabetic control subjects [24], we had not measured maternal serum ferritin concentration at the time of the OGTT in the women with thalassaemia traits. The hypothesis that iron excess plays a role in the development of GDM in these women must therefore be speculative.

Iron excess might not be the only explanation of the high prevalence of GDM in women with α-thalassemia trait, because pancreatic α-cell overactivity with increased glucagon response has also been shown in thalassaemic patients with impaired glucose tolerance [25]. It is possible that there are other subtle metabolic disturbances associated with α-thalassemia trait that could predispose a pregnant women to the development of GDM but the pathophysiological mechanism of GDM in women with α-thalassemia trait remains to be elucidated.

Of note, there was no difference in the obstetric or perinatal outcome between the study and control groups, despite the difference in the prevalence of GDM. It was possible that as the great majority of women with GDM had the WHO category of IGT, diet treatment had normalised glycaemic control and hence pregnancy outcome. Nonetheless, the GDM pregnancies in the study group had a 17% incidence of LGA infants despite a lower infant BMI. It was also possible that the effect of GDM had cancelled

out any unfavourable effect of the haemoglobinopathy on the pregnancy. A third possibility was that the abnormal OGTT was a reflection of the insulin resistance state in women with α-thalassaemia trait rather than the diabetogenic effect of their pregnancies. Thus their pregnancy outcome might actually be better than that in GDM women without the thalassaemia trait. This might have explained the lower incidence of women aged 35 years or older, as well as the trend of lower incidence of infant macrosomia, phototherapy for jaundice, and metabolic complications, which failed to reach statistical significance because of the small numbers.

Our findings indicate that in Hong Kong, the incidence of α-thalassaemia trait in women at risk of GDM (4.9%) was similar to the 5% incidence of α-thalassaemia trait in the overall population in our locality [12]. However, the presence of α-thalassaemia trait significantly increases the likelihood of GDM. Although there is as yet no long-term follow-up studies on women with the α-thalassaemia trait, they are probably also at increased risk for the later development of diabetes mellitus.

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