ORIGINAL ARTICLE

Re-emergence of late presentations of fetal haemoglobin Bart's disease in Hong Kong

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Objectives To compare early and late presentations of fetal haemoglobin Bart's disease in the Kowloon West Cluster in Hong Kong, and to find reasons for the re-emergence of late presentations.

Design Case series with internal comparisons.

Setting Two tertiary obstetric units in Hong Kong.

Patients All cases with confirmed diagnosis of fetal haemoglobin Bart's disease from 1 January 2000 to 31 December 2009.

Main outcome measures Primary outcome: antenatal care in the current pregnancy. Secondary outcomes: clinical presentations, ultrasound features, and pregnancy outcomes.

Results A total of 59 cases (46 early presentations and 13 late presentations) of fetal haemoglobin Bart's disease were identified during the study period. All the late presentations were identified from year 2003 onwards. Late presentations were significantly associated with non-eligible obstetric patients (69% vs 11%; P<0.001), non-booked status at our antenatal service (62% vs 0%; P<0.001), and unavailability of partner's mean corpuscular volume status (23% vs 0%; P=0.009). Mothers presenting late were more likely to have symptoms or signs (85% vs 0%; P<0.001) and to suffer from gestational hypertensive disorder (54% vs 0%; P<0.001). Ultrasound features of these pregnancies included cardiomegaly (94%), placentomegaly (98%), and hydrops fetalis (77%). All pregnancies presenting early were either legally terminated or miscarried. The perinatal mortality in late presentations was 85%.

Conclusion The re-emergence of late presentations of fetal haemoglobin Bart's disease after 2003 was related to influx of non-eligible obstetric patients without proper antenatal screening and diagnosis of thalassaemia. Maternal low mean corpuscular volume and characteristic prenatal ultrasound features such as cardiomegaly, placentomegaly, and hydrops fetalis are useful for detecting affected pregnancies in this group of patients. Better education of both patients and doctors is necessary to explain the importance of early diagnosis of the disease and the seriousness of complications due to late presentations, so as to reduce undesirable maternal and perinatal outcomes.

Key words
alpha-Thalassemia; Congenital abnormalities; Hemoglobins, abnormal; Hydrops fetalis; Prenatal diagnosis

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New knowledge added by this study

- Re-emergence of late presentations of fetal haemoglobin Bart's disease in Hong Kong after 2003 is related to an influx of obstetric patients who had not undergone proper antenatal screening and diagnosis of thalassaemia.
- Reasons for not making the diagnosis in early pregnancy included: late or no booking at our antenatal services, defaulting of follow-up, improper implementation of screening or diagnostic procedures, and possibility of non-paternity.

Implications for clinical practice or policy

- Maternal low mean corpuscular volume (MCV) and characteristic prenatal ultrasound features (cardiomegaly, placentomegaly, and hydrops fetalis) are useful for detecting affected pregnancies in this group of patients; a late-booked woman with a low MCV and suspected fetal haemoglobin Bart's disease should be referred to a maternal fetal medicine specialist for ultrasound assessment and consideration of diagnostic testing.
- Better patient and doctor education is needed both in Mainland China and Hong Kong to stress the importance of early diagnosis and the serious sequelae of presenting late.

Introduction

Haemoglobin (Hb) Bart's disease, also known as homozygous alpha^0-thalassaemia, is an autosomal recessive disorder characterised by absence of all four alpha genes.[1] When both parents carry alpha^0-thalassaemia traits, there is a 25% chance that their offspring will suffer from Hb Bart's disease. Affected pregnancies are associated with both adverse maternal and perinatal outcomes. Severe anaemia in-utero can result in hydrops fetalis, limb reduction defects, stillbirth, and neonatal death.[2-4] Mothers carrying such hydropic fetuses have a higher risk of pre-eclampsia, antepartum haemorrhage, dystocia, retained placenta, and postpartum haemorrhage.[1,2,5]

Alpha^0-thalassaemia carrier status is common in our locality, with a prevalence of 5% in Hong Kong, 4% in Guangdong province, and 15% in Guangxi province of China.[6] Fortunately, since 1983 routine antenatal thalassaemia screening using mean corpuscular volume (MCV) of ≤80 fL and prenatal diagnosis have successfully reduced the incidence of fetal Hb Bart's disease in Hong Kong.[7,8] The affected pregnancies are usually terminated, and hence it is rare to see Hb Bart's fetuses going into the third trimester of pregnancy.[9]

However, there has been a re-emergence of late presentations of fetal Hb Bart's disease in recent years. The aim of this study was to compare the demographics, clinical features, and outcomes of early and late presentations of fetal Hb Bart's disease in two local tertiary obstetric units. By this means it might be possible to explain the re-emergence of late presentations of fetal Hb Bart's disease in Hong Kong, and make recommendations to minimise such undesirable outcomes.

香港重現胎兒血紅蛋白Bart's症遲診的病例

目的 比較香港九龍西醫院聯網中胎兒血紅蛋白Bart's症早診和遲診的病例，並探討香港重現此症遲診的原因。

設計 病例系列中案例的比較。

安排 香港兩個三級產科部門。

患者 2000年1月1日至2009年12月31日期間所有確診為胎兒血紅蛋白Bart's症的病例。

主要結果測量 主要結果為該次懷孕的產前檢查；次要結果為臨床表現、超聲波特徵和妊娠結果。

結果 研究期間共有59宗胎兒血紅蛋白Bart's症的病例，其中46宗屬早診病例，其餘13宗為遲診病例。所有遲診病例均在2003年後發生。遲診病例與以下三項明顯相關：非符合資格產科病人（69%比11%；P<0.001）、並未在產前服務處預約登記者（62%比0%；P<0.001）、及未有檢驗配偶平均紅血球體積者（23%比0%；P=0.009）。遲診病例的婦女出現胎兒血紅蛋白Bart's症的病徵或症狀的可能性較高（85%比0%；P<0.001），並有更大機會患上妊娠期高血壓綜合症（54%比0%；P<0.001）。這些病例的超聲波特徵包括心臟發大（94%）、胎盤脹大（98%）和胎兒水腫（77%）。所有早診病例均自然流產或終止妊娠。遲診病例的圍產兒死亡率為85%。

結論 2003年後胎兒血紅蛋白Bart's症的遲診病例重現，主要與非符合資格產科病人的增加有關，她們未有進行適當的產前地中海貧血症篩查及診斷。要為這些孕婦檢測是否有胎兒血紅蛋白Bart's症，她們較小的平均紅血球體積，以及產前超聲波特徵如心臟發大、胎盤脹大和胎兒水腫都很有用。須讓病人和醫生知道及早診斷胎兒血紅蛋白Bart's症的重要性，以及了解因遲診而引致嚴重併發症的後果以減低孕婦和胎兒的不良結果，教育是關鍵 。

Methods

This study entailed collecting data on all cases of fetal Hb Bart's disease diagnosed in two tertiary obstetric units in the Kowloon West Cluster of Hong Kong, namely at Princess Margaret and Kwong Wah hospitals. Two subgroups were compared: early and late presentations of fetal Hb Bart's disease. 'Early' was defined as prenatal diagnosis made in the first or second trimester of pregnancy (≤24 weeks), and 'late' was defined as diagnosis made in the third trimester of pregnancy (>24 weeks) or in the perinatal period.

A 10-year study period from 1 January 2000 to 31 December 2009 was chosen. All cases with confirmed diagnosis of fetal Hb Bart's disease within the study period were included. The cases were identified from the database of the Prenatal Diagnosis Clinics (PDC) of the two obstetric units. The hospital records, out-patient records, and PDC records of the cases were reviewed. All cases had the diagnosis of fetal Hb Bart's disease confirmed, either by genetic study (chorionic villus sampling or amniocentesis) performed in the molecular laboratory of the University of Hong Kong, or by Hb pattern analysis (cordocentesis, cord blood, or neonatal blood); presence of ≥70% Hb Bart's was taken as confirming the diagnosis.

The main clinical characteristics being studied were antenatal care in the current pregnancy, which comprised eligibility of the obstetric patients, their booking status at our antenatal service, the gestation of pregnancy at the time of booking, availability of antenatal MCV status, and availability of partner's MCV status. The secondary outcome measures included clinical presentations, ultrasound features, and pregnancy outcomes. The clinical presentations studied were gestational hypertensive disorder and other presenting features. Gestational hypertensive disorder included the spectrum of gestational hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, on two occasions at least 4 hours apart),

gestational proteinuria (≥1+ protein on urine dipstick test), or both. The ultrasound features studied were cardiomegaly (cardiothoracic ratio ≥0.5),[10] placentomegaly (placental thickness ≥mean + two standard deviations [SDs]),[11] liquor volume, and hydrops fetalis. Ultrasound evaluation was performed by specialist obstetricians of the Maternal Fetal Medicine teams of the two units. Cardiothoracic ratio was measured by obtaining the four-chamber view of the fetal heart, measuring the transverse cardiac diameter between the epicardial surfaces at the level of atrioventricular valves at diastole, and the transverse thoracic diameter. The ratio was calculated by dividing the transverse cardiac diameter by the transverse thoracic diameter. Placental thickness was measured by putting the transducer perpendicular to the placenta, and taking the average of measurements at the centre in longitudinal and transverse sections. Pregnancy outcomes were classified as termination of pregnancy, miscarriage, stillbirth, neonatal death, or live birth.

TABLE 1. Demographics and aspects of antenatal care in the current pregnancy of early and late presentations of fetal haemoglobin Bart's disease*

Demographics	All (n=59)	Early (n=46)	Late (n=13)	P value†
Age (years)	30 ± 6	30 ± 6	29 ± 5	0.298
Parity				0.189
Nulliparous	38 (64%)	32 (70%)	6 (46%)	
Multiparous	21 (36%)	14 (30%)	7 (54%)	
Non-eligible person	14 (24%)	5 (11%)	9 (69%)	<0.001
Non-booked case	8 (14%)	0 (0%)	8 (62%)	<0.001
Gestation at booking (weeks)	12 (9-17)	11 (9-13)	28 (13-30)	0.005
Antenatal MCV‡ available	58 (98%)	46 (100%)	12 (92%)	0.220
Partner's MCV available	56 (95%)	46 (100%)	10 (77%)	0.009

* Data are shown as No. (%), mean ± standard deviation, or median (interquartile range)
† Comparison of early and late presentations
‡ MCV denotes mean corpuscular volume

Statistical analyses

Skewed continuous variables and near normally distributed variables were presented as medians (interquartile ranges [IQRs]) and means (SDs), respectively. Categorical data were presented as counts and percentages. The Mann-Whitney *U* test and the independent samples *t*-test were used for comparison of medians and means, respectively. The Pearson Chi squared test or Fisher's exact test were used for comparison of frequencies where appropriate. The pregnancy outcomes in the two

TABLE 2. Summary of the late presentations of fetal haemoglobin Bart's disease*

Case No.	Gestation at diagnosis (weeks)	Eligible person	Booked case	Partner's MCV available	Gestational hypertensive disorder	Ultrasound features				Outcome	Remarks
						Cardiomegaly	Placentomegaly	Liquor volume	Hydrops fetalis		
1	35	×	✓	✓	×	-	-	-	-	NND	Booked at 28 weeks, then defaulted
2	38	×	✓	×	✓	-	-	-	-	NND	Booked at 29 weeks, then defaulted
3	33	×	×	✓	×	✓	✓	Normal	-	LB	No prenatal diagnosis after PGD
4	32	✓	×	✓	×	✓	✓	Normal	✓	SB	Alpha^0-thalassaemia trait known in private but partner's MCV not checked
5	32	✓	✓	✓	✓	✓	✓	Decreased	✓	NND	Low MCV couple known in China but no prenatal diagnosis; booked at 30 weeks; IUGR
6	34	✓	✓	✓	×	✓	✓	Increased	✓	NND	Partner's MCV normal†
7	28	✓	✓	✓	×	✓	✓	Decreased	✓	SB	Partner's MCV normal†; IUGR
8	35	×	×	✓	✓	-	-	-	-	LB	Partner's MCV normal†
9	35	×	×	✓	✓	✓	✓	Normal	✓	NND	Eclampsia
10	34	×	×	×	✓	✓	✓	Decreased	✓	NND	IUGR
11	37	×	×	×	✓	✓	✓	Normal	✓	NND	Recurrent case
12	26	×	×	✓	×	✓	✓	Normal	✓	NND	-
13	35	×	×	✓	✓	✓	✓	Normal	✓	NND	-

* ✓ denotes positive or presence of the feature and × negative or absence of the feature, IUGR intrauterine growth restriction, LB live birth, MCV mean corpuscular volume, NND neonatal death, PGD pre-implantation genetic diagnosis, and SB stillbirth
† Raises questions as to paternity

groups were described. All analyses were performed with the Statistical Package for the Social Sciences (Windows version 17.0; SPSS Inc, Chicago [IL], US). The statistical significance level was set at a P value of less than 0.05.

Ethics approval

Ethics approval for this study was granted by the Kowloon West Cluster Clinical Research Ethics Committee (KW/EX/10-089 [31-17]).

Results

A total of 59 cases (46 early and 13 late) of fetal Hb Bart's disease were identified during the study period. All the late cases were identified from year 2003 onwards, while the number of early cases remained static over the entire study period. For the early group, the median (IQR) gestation at diagnosis was 17 (range, 12-18) weeks, while that for the late group was 34 (32-35) weeks. The mean (SD) age was 30 (6) years for the early group and 29 (5) years for the late group (P=0.298). There was no statistically significant difference between the two groups in terms of parity and availability of antenatal MCV status (Table 1).

The late as opposed to early presentations were significantly associated with non-eligible obstetric patients (69% vs 11%; P<0.001), non-booked status at our antenatal service (62% vs 0%; P<0.001) and unavailability of partner's MCV status (23% vs 0%; P=0.009). For the late group, among those who were booked at our antenatal service, the median (IQR) gestation at the time of booking was 28 (13-30) weeks, while that for the early group was 11 (9-13) weeks (P=0.005) [Table 1]. In the late group, early diagnosis was not made in two booked cases, because the mothers defaulted (Table 2: cases 1 and 2). In three other late cases, the diagnosis was missed in early pregnancy because proper prenatal screening or diagnosis of fetal Hb Bart's disease was not undertaken (Table 2: cases 3, 4 and 5). One of them was after pre-implantation genetic diagnosis for alpha^0-thalassaemia (Table 2: case 3). For three other cases in the late group, their partner's MCV were normal (Table 2: cases 6, 7, and 8).

None of the mothers in the early group presented with symptoms or signs, while 11 (85%) out of 13 mothers in the late group had clinical presenting features (P<0.001). Seven (54%) out of 13 pregnancies in the late group were complicated by gestational hypertensive disorder, including one case of eclampsia (Table 2: Case 9). The other clinical presentations are summarised in Table 3.

Except for liquor volume, there was no statistically significant difference between the two groups for all the other ultrasound features under study. Some data were missing because not every case in the study had a comprehensive documentation of each of the ultrasound features. With the available data, cardiomegaly was present in 45 (94%) out of 48 cases, placentomegaly in 41 (98%) out of 42 cases, and hydrops fetalis in 26 (77%) out of 34 cases. The liquor volume was normal in 32 (84%) out of 38 cases, increased in three (8%) of them, and reduced in the remaining three (8%) [Table 4].

There were four silent miscarriages in the early group. One was diagnosed 1 day after attempted cordocentesis. All the remaining 42 pregnancies underwent termination after counselling. In the late group, there were nine neonatal deaths and two

TABLE 3. Clinical features of early and late presentations of fetal haemoglobin Bart's disease

Clinical feature	No. (%)			P value*
	All (n=59)	Early (n=46)	Late (n=13)	
Presence of symptoms or signs	11 (19)	0 (0)	11 (85)	<0.001
Gestational hypertensive disorder	7 (12)	0 (0)	7 (54)	<0.001
Other presentations		-	-	-
Reduced fetal movement	2 (3)		2 (15)	
Uterus smaller than date	2 (3)		2 (15)	
Fetal distress	2 (3)		2 (15)	
Fetal ascites	1 (2)		1 (8)	

* Comparison of early and late presentations

TABLE 4. Ultrasound features of early and late presentations of fetal haemoglobin Bart's disease

Ultrasound feature	No. (%)			P value*
	All	Early	Late	
Cardiomegaly	45/48 (94)	35/38 (92)	10/10 (100)	1.000
Placentomegaly	41/42 (98)	31/32 (97)	10/10 (100)	1.000
Liquor volume				0.009
Normal	32/38 (84)	26/28 (93)	6/10 (60)	
Increased	3/38 (8)	2/28 (7)	1/10 (10)	
Decreased	3/38 (8)	0/28 (0)	3/10 (30)	
Hydrops fetalis	26/34 (77)	17/25 (68)	9/9 (100)	0.077

* Comparison of early and late presentations

TABLE 5. Pregnancy outcomes of early and late presentations of fetal haemoglobin Bart's disease

Pregnancy outcome	No. (%)	
	Early (n=46)	Late (n=13)
Termination of pregnancy	42 (91)	-
Silent miscarriage	4 (9)	-
Stillbirth	-	2 (15)
Neonatal death (<1 month)	-	9 (69)
Live birth (survived >1 year)	-	2 (15)

stillbirths, constituting a perinatal mortality of 85%. The remaining two were live births who survived with morbidities (Table 5). One was 51 months old at the time this report was prepared, and was undergoing regular blood transfusions every 5 weeks (Table 2: case 8). She had global developmental delay, hypoplastic fingers with syndactyly, and hypoplastic forefeet requiring physiotherapy and occupational therapy. The other was 19 months old and had cerebral palsy, hypospadias and micropenis, and was also undergoing regular blood transfusions (Table 2: case 3).

Discussion

Fetal Hb Bart's disease is a common genetic disorder that should be diagnosed in the early antenatal period. In Hong Kong, with a well-established universal antenatal screening system for thalassaemia couples and prenatal diagnosis, it is not surprising that the number of early presentations of fetal Hb Bart's disease far exceeds late presentations.

All cases in our late diagnosis group were identified from year 2003 onwards. Ever since the Court of Appeal's decision in 2001 on the Right of Abode and the Individual Visit Scheme in 2003, an increasing number of non-eligible obstetric patients had travelled from mainland China to deliver their babies in Hong Kong, so that their children would have residency rights.[9] This has created a social obstetrics phenomenon, whereby standard obstetrics practice is affected by a socioeconomic situation. Because of their non-eligible status, these mothers had to pay much higher fees to use the public health services in Hong Kong. As a result, many of them did not book our antenatal service. This study showed that both non-eligibility and non-booked status were significantly associated with the late presentations of fetal Hb Bart's disease. Even if these mothers did book at our antenatal service, because of financial reason again, they often did so late and defaulted regular antenatal visits. In our late-diagnosis group, there were booked cases with known low antenatal MCV, but further investigations could not be carried out because the mothers had defaulted, and only returned in late pregnancy when they had become symptomatic (Table 2: cases 1 and 2). In this study, the non-availability of the partner's MCV status was significantly associated with late presentations of fetal Hb Bart's disease, and could be attributed to this breakdown in the continuity of antenatal care.

Some non-eligible mothers chose to have antenatal care in mainland China. Regrettably, the practice of antenatal care in mainland China might not be the same as that in Hong Kong. There was a case in our late-diagnosis group where the couple was known to have low MCV, but no further investigation was undertaken (Table 2: case 5). Even worse, some of these mothers avoided antenatal care in mainland China in order to evade the one-child policy.[9] Notably, some mothers in our late-diagnosis group received prior antenatal care in the Hong Kong private sector, but the diagnosis of fetal Hb Bart's disease was nevertheless missed in early pregnancy. One mother had low MCV, but her partner's MCV status was not checked (Table 2: case 4). Another instance involved a known alpha^0-thalassaemia couple. They had received in-vitro fertilisation in the private sector and pre-implantation genetic diagnosis was performed for alpha^0-thalassaemia. Amniocentesis had been done for advanced maternal age, but the alpha gene was not checked (Table 2: case 3). Prenatal diagnosis of fetal Hb Bart's disease (either by ultrasound monitoring or invasive tests) should therefore still be carried out after a pre-implantation genetic diagnosis for alpha^0-thalassaemia.

There were two patients in our late-diagnosis group who did book early and underwent routine antenatal thalassaemia screening. Although they had a low MCV, the diagnosis of fetal Hb Bart's disease was not entertained early as their partner's MCVs were normal (Table 2: cases 6 and 7). One of them presented at 28 weeks' gestation with severe early-onset intrauterine growth restriction, and the other at 34 weeks with fetal distress and poor condition of the neonate at birth. Both offspring were confirmed to have fetal Hb Bart's disease. Both cases raised the possibility of non-paternity, as the partners had normal MCVs when checked by antenatal thalassaemia screening. One of these couples underwent alpha gene study to rule out the rare possibility of any non-deletional alpha gene abnormality, but again the result on the partner showed no abnormality. Together with another non-booked case (Table 2: case 8), non-paternity was a possibility in three (23%) out of 13 of our late subgroup cases. Thus, the diagnosis of fetal Hb Bart's disease should still be considered if ultrasound or clinical features are suggestive, regardless of the partner's MCV. Moreover, inadvertent discovery of non-paternity during workup for genetic disease has also been reported in the literature.[12]

If not miscarried, all pregnancies with fetal Hb Bart's disease diagnosed early were terminated before any maternal or fetal complications arose. Not surprisingly, only patients in the late group presented with clinical symptoms or signs. Non-eligible mothers, who had the tendency to seek help at the last minute because of financial considerations, presented only when symptomatic, at which time complications of fetal Hb Bart's disease had already set in. Liang et al[5] reported 61% of 46 cases in their series to suffer from hypertension or pre-eclampsia, while Tan et al[13] reported 20% of 25 cases in their series. In our study, 54% of 13 pregnancies in the late-diagnosis group were complicated by gestational hypertensive disorder. There was one case of eclampsia that

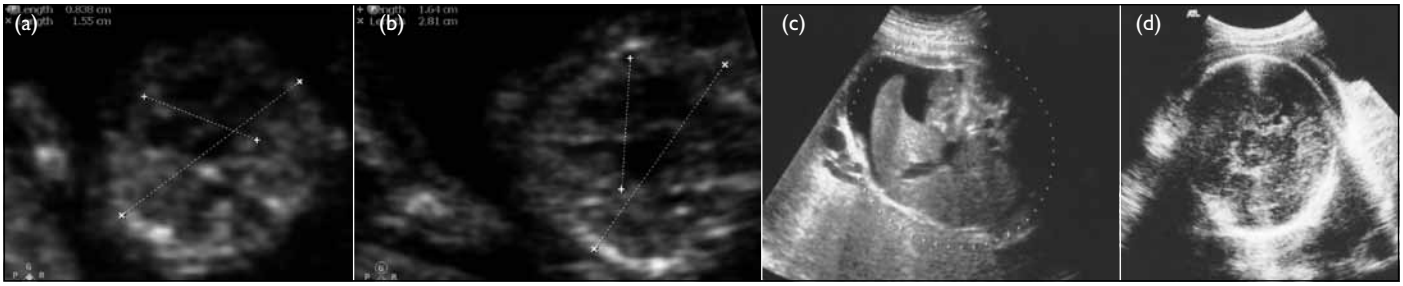

FIG. Ultrasound features of fetal haemoglobin Bart's disease
(a) Cardiomegaly at 12 weeks. (b) Cardiomegaly at 18 weeks. (c) Hydrops fetalis—fetal ascites. (d) Hydrops fetalis—scalp oedema

presented at 35 weeks of gestation with a blood pressure of 200/110 mm Hg and 3+ proteinuria (Table 2: case 9). That mother was admitted to the Intensive Care Unit for cerebral oedema.

Notably, there were no statistically significant differences between the early and late groups for most of the ultrasound features, as the ultrasound features of Hb Bart's fetuses can be detected early in pregnancy (Fig). Using a cardiothoracic ratio cut-off of ≥0.5 for cardiomegaly, Lam et al[10] reported 100% sensitivity and 100% specificity for the detection of Hb Bart's fetuses at 12 to 13 weeks gestation. Leung et al[14] suggested that fetal cardiothoracic ratio increased with gestational age, and therefore its predictive value in pregnancies affected by fetal Hb Bart's disease also varied with gestation, with an overall sensitivity of 100% and specificity of 95.6%. The cut-off should be increased with gestational age to reduce the false-positive rate. Placentomegaly was another ultrasound feature of Hb Bart's fetuses that has been studied. Using a placental thickness cut-off of ≥mean + 2 SDs for such testing, Ghosh et al[11] reported 72% sensitivity and 97% specificity before 12 weeks, 95% sensitivity and 96% specificity after 12 weeks, and 100% sensitivity and 96% specificity after 18 weeks. Liquor volume could be normal, increased, or reduced in Hb Bart's fetuses, and hence it should not be relied on for their detection. Polyhydramnios was reported in 59% of 46 cases by Liang et al[5] and 52% of 25 cases by Tan et al.[13] Oligohydramnios has also been reported in three cases (at 21, 23, and 25 weeks) by Leung et al.[15] Notably the three cases of oligohydramnios in our study were those complicated by severe intrauterine growth restriction noted at 28, 32, and 34 weeks respectively (Table 2: cases 5, 7, and 10).

Affected pregnancies are usually terminated because of the associated maternal and perinatal morbidities, even though fetal Hb Bart's disease is no longer considered an absolutely non-salvageable condition. There have been case reports of survivors with intrauterine transfusions, postnatal regular blood transfusions, bone marrow transplant, and mismatched sibling cord blood transplant.[15-18] Lee et al[19] reported six Hb Bart's infants without prior intrauterine therapy receiving intensive care in a local tertiary paediatric unit. While five of them succumbed, one survived with normal neurological outcome. In our study, there were two survivors (Table 2: cases 3 and 8). Both of them were delivered on the day of admission. The diagnosis of Hb Bart's disease was made after delivery, and neither of them had received any intrauterine therapy. Both of them received regular blood transfusions and endured developmental delay. The limb reduction defect in one baby and hypospadias in the other could be explained by the in-utero hypoxic insult early on during gestation.[3,20,21]

In our study, there were recurrent pregnancies affected by fetal Hb Bart's disease. Although not a statistically studied outcome, eligible couples tended to seek early prenatal diagnosis in their subsequent pregnancies, while one non-eligible mother presented in the third trimester twice for her two consecutively affected pregnancies, despite counselling on the nature and recurrence risk of the disease after the first encounter (Table 2: cases 10 and 11). During her second pregnancy, she did undergo some form of antenatal ultrasound screening for fetal Hb Bart's disease in mainland China, but the diagnosis was missed. This might reflect the different attitudes towards antenatal care in mainland China and Hong Kong, and the variable standards of antenatal care that prevail.

Regarding limitations to this study, being retrospective, some data like the ultrasound features were not comprehensive. Second, the number of late presentations identified was small, which could be attributed to the rarity of the condition. Third, the ethical and psychological issues of prenatal diagnosis and management of fetal Hb Bart's disease have not been discussed, as they were considered beyond the scope of this study. Nonetheless, they could become increasingly important, especially if Hb Bart's disease might become potentially curable with advances in technology.

Conclusion

The re-emergence of late presentations of fetal Hb Bart's disease after 2003 was related to an influx of non-eligible obstetric patients without proper antenatal screening and diagnosis of thalassaemia. The reasons for not arriving at a diagnosis in early pregnancy included: late or no booking at our antenatal service, defaulting follow-up, improper implementation of screening or diagnostic procedures, and the possibility of non-paternity. Unfavourable pregnancy outcomes associated with late presentations of fetal Hb Bart's disease included gestational hypertensive disorder, eclampsia, stillbirths or neonatal death, and long-term neonatal morbidities. Maternal low MCV and characteristic prenatal ultrasound features such as cardiomegaly, placentomegaly, and hydrops fetalis are useful for the detection of such pregnancies. A late-booking woman with a low MCV and suspected fetal Hb Bart's disease should be referred to a Maternal Fetal Medicine specialist for ultrasound assessment and consideration of invasive diagnostic testing. Better education of patients and doctors, both in mainland China and Hong Kong, is necessary to raise awareness about the importance of early diagnosis and the serious complications of late presentation. By this means, undesirable maternal and perinatal outcomes may be avoided.

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