

# Outcomes and morbidities of patients who survive haemoglobin Bart's hydrops fetalis syndrome: 20-year retrospective review

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## ABSTRACT

**Introduction:** Haemoglobin Bart's hydrops fetalis syndrome was once considered a fatal condition. However, advances over the past two decades have enabled survival of affected patients. Data relating to their morbidities and outcomes will help medical specialists formulate a management plan and parental counselling.

**Methods:** All babies with the syndrome who survived beyond the neonatal period and were subsequently managed long-term in eight public hospitals in Hong Kong from 1 January 1996 to 31 December 2015 were included. Patient and parent characteristics, antenatal care, reasons for continuation of pregnancy, intrauterine interventions, perinatal course, presence of congenital malformations, stem-cell transplantation details, and long-term neurodevelopmental outcomes were reviewed.

**Results:** A total of nine patients were identified, of whom five were female and four male. The median follow-up duration was 7 years. All were Chinese and were homozygous for the Southeast Asian  $\alpha$ -thalassaemia deletion. Five of the nine mothers received antenatal care at a public hospital and opted to continue the pregnancy after antenatal diagnosis and counselling. Despite intrauterine transfusions, all babies were born with respiratory depression and required intubation and mechanical ventilation during the neonatal period. Hypospadias was identified in all four male infants. Growth retardation, global developmental delay, and residual

neurological deficits were noted in two-thirds of the patients. Haematopoietic stem-cell transplantation was performed in two patients, who became transfusion-independent.

**Conclusions:** Survival of patients with Bart's hydrops fetalis syndrome is possible but not without short- and long-term complications; local epidemiology is comparable to that documented for an international registry. Detailed antenatal counselling of parents with a non-judgemental attitude and cautious optimism are imperative.

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### New knowledge added by this study

- This is the first territory-wide multicentre retrospective review of demographic data, morbidities, and outcome of survivors of haemoglobin Bart's hydrops fetalis syndrome in Hong Kong.
- Intrauterine transfusion is commonly practised in local obstetric units in an attempt to reduce fetal hypoxia and fetal-maternal complications, presumably contributing to survival.
- Prematurity and perinatal respiratory depression are often encountered; intubation, mechanical ventilation, and exchange transfusions are beneficial. Regular hypertransfusion and optimal iron chelation are advocated. Haematopoietic stem-cell transplantation is curative but morbidities and mortalities should not be overlooked.

### Implications for clinical practice or policy

- Better patient and doctor education is needed, stressing the importance of early accurate diagnosis and the serious sequelae of late presentation.
- Diagnosis should be considered if ultrasonographic features are clinically suggestive, regardless of parents' mean corpuscular volume, owing to uniparental disomy or non-paternity. Clinical vigilance and prompt specialist referral for ultrasonography and accurate diagnostic testing are crucial to improve maternal-fetal outcomes.
- For parents who opt to continue the pregnancy after diagnosis, meticulous counselling about perinatal and long-term outcomes and morbidities of survivors is imperative.
- Multidisciplinary anticipatory care among obstetricians, pathologists, neonatologists, and haematologists promotes survival, lowers morbidity, and improves long-term outcomes. Patients can now survive beyond childhood, so adult-care physicians can expect to encounter an increasing number of referrals of adult survivors of haemoglobin Bart's hydrops fetalis syndrome.

## 香港過去二十年巴特氏血紅蛋白胎兒水腫綜合徵（甲型重型地中海貧血）存活者的回顧性研究

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**引言：**巴特氏血紅蛋白胎兒水腫綜合症（BHFS），亦稱純合子甲型重型地中海貧血，曾一度被認為是會引致胎死腹中的致命疾病。不過，隨着過去二十年香港在產前診斷、胎兒宮內輸血和新生兒深切治療各方面的進步，患病的胎兒得以存活，甚至長大成人。從本研究中所得到的資料，將有助本港產科和兒科醫生輔導病兒的家長和規劃病兒出生後的護理。

**方法：**所有在1996年1月1日至2015年12月31日期間被診斷患有巴特氏血紅蛋白胎兒水腫綜合症的嬰兒（無論是在產前或出生後才被確診），並在香港公立醫院出生及繼續在兒科接受長期覆診的存活者，都被納入這項研究中。母嬰的基本資料、產前超聲波檢查結果、產前診斷報告、繼續妊娠的原因、宮內輸血的資料、新生兒的護理、嬰兒先天畸形及往後長期的神經和智能發展、以及血幹細胞移植的應用和結果等數據都被收集分析。

**結果：**共有9名患者（4男5女），平均年齡為7歲。所有患者均為中國人，全被鑑定擁有純合子東南亞型基因（SEA）缺失。其中五名孕婦在香港公立醫院接受產前護理，全都在產前診斷出甲型重型地貧，並進行兩至四次宮內輸血。所有4個男性胎兒均有尿道下裂的情況。三分之二患兒有生長和發展遲緩問題或神經系統受損。接受骨髓移植的兩例都是在大約20個月大時進行的。他們都移植成功，完全治癒，不用長期輸血。

**結論：**總而言之，甲型重型地貧患者的生存是可能的，但有短期和長期併發症。本地流行病學的數據與國際數據相當。在輔導甲型重型地貧患者的準父母時應保持開放及審慎樂觀的態度，並提供適切的協助。

## Introduction

Haemoglobin Bart's hydrops fetalis syndrome (BHFS), also known as homozygous  $\alpha^0$ -thalassaemia major or homozygous  $\alpha$ -thalassaemia 1, was first described in 1960.<sup>1,2</sup> It was considered fatal in the 1960s to 1970s,<sup>3</sup> and fetuses often died in utero, were stillborn or died during the early neonatal period.<sup>4</sup> When prenatal screening and diagnosis for thalassaemia first started in Hong Kong in 1983, BHFS was advocated as an indication for termination of pregnancy.<sup>5</sup> Nonetheless, the availability of intrauterine transfusions (IUTs)<sup>6,7</sup> and intrauterine exchange transfusions (IUEs) enabled affected fetuses to survive the perinatal period.

Since the world's first reported case of survival in 1985 in Canada,<sup>8</sup> increasing numbers of BHFS survivors have been reported worldwide, including in Hong Kong.<sup>9</sup> The traditional view of its fatality has been challenged,<sup>10,11</sup> and in the 1990s there was lively debate about the ethical concerns surrounding active resuscitation and treatment of BHFS babies. Regular transfusions and iron chelation allow BHFS patients to survive even beyond adulthood, and haematopoietic stem cell transplantation<sup>12-14</sup> offers a cure for this

disease, albeit at the expense of possible significant morbidities and compromised quality of life. Long-term morbidities for this cohort of patients thus become an important issue to address. Information gathered by this territory-wide retrospective study will assist physicians in contemplating perinatal management and counselling of parents.

## Methods

### Data collection

The setting for this study was all eight public hospital paediatric haematology units in Hong Kong that care for patients with transfusion-dependent thalassaemia. Records of patients diagnosed with BHFS (either antenatally or postnatally) who survived beyond the neonatal period and who were subsequently managed long-term at those units from 1 January 1996 to 31 December 2015 were retrieved from the Hong Kong Hospital Authority's Clinical Data Analysis and Reporting System using the International Classification of Diseases diagnostic code 282.7, searching only for Haemoglobin-Bart's disease. Data cross-checking was performed with the help of the Hong Kong Paediatric Haematology and Oncology Study Group and paediatric haematologists from the eight hospitals.

Information about patient and parent characteristics, availability of antenatal care and diagnosis, antenatal ultrasonographic findings, reasons for continuation of pregnancy, use of intrauterine transfusions, perinatal course, presence of congenital malformations, subsequent neonatal and long-term neurodevelopmental outcome, and availability of stem-cell transplantation and subsequent outcomes were collected and studied. Patients with BHFS who were not born in Hong Kong were excluded from this study. No missing cases were identified during the 20-year study period, as confirmed from personal communications with both paediatric and adult haematologists from all public hospitals in Hong Kong. As BHFS pregnancies are considered high risk owing to possible maternal-fetal complications, it was presumed that no cases would have been managed by private doctors without support from a neonatal intensive care unit.

### Statistical analyses

This study was primarily descriptive in nature. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk [NY], United States). Continuous variables are expressed as median and range.

### Ethics approval

This study complied with the Declaration of Helsinki and approval was obtained from the Institutional

Review Board of The University of Hong Kong / Hong Kong Hospital Authority West Cluster and all other clusters of participating hospitals. Verbal (parental) consent was obtained but formal written consent was not required by the institutional review board, as this retrospective study did not involve direct patient care (Ref No. HKUCTR-2148).

## Results

### Demographic and genetic features

Surviving patients with BHFS were identified in five of the eight local paediatric haematology units. A total of nine infants were found, of whom five were female and four male. All patients were Chinese, and all were confirmed to be homozygous for the Southeast Asian  $\alpha$ -thalassaemia deletion. Six pairs of parents were heterozygous for the Southeast Asian deletion, and three pairs refused genetic testing, one of which was suspected to be a case of non-paternity (case 7). For case 6, the mother was heterozygous for the Southeast Asian deletion ( $\alpha$ -thalassaemia 1), whereas the father had an  $\alpha$ 3.7 single deletion ( $\alpha$ -thalassaemia 2). The child demonstrated maternal uniparental disomy and isodisomy (Tables 1 and 2).<sup>6,13-20</sup>

### Prenatal diagnosis, intrauterine management, and maternal complications

Among the nine mothers, one received no antenatal care, two received antenatal care in a local private centre, and one received antenatal care in mainland

China. All were considered normal and received no IUT. For the remaining five mothers who received antenatal care in a public hospital, all had BHFS diagnosed antenatally in their neonates (two by cordocentesis, one by chorionic villus sampling, one by amniocentesis, and one by both cordocentesis and chorionic villus sampling). All five couples decided to continue the pregnancy after counselling: two for religious reasons and three out of personal preference. All five patients had IUT/IUET performed two to four times. Antenatal ultrasonography of seven fetuses revealed cardiomegaly in four and hydropic changes in two, one of which subsequently resolved after IUT. Placentomegaly was detected in three mothers and polyhydramnios in one. Pre-eclampsia was reported in two mothers and was controlled with antihypertensive drugs (Tables 2 and 3).<sup>6,13-20</sup>

### Neonatal outcomes and co-morbidities

Preterm delivery occurred in seven of the nine cases, with a median gestational age at delivery of 33 weeks. All infants had respiratory depression at birth and required resuscitation, neonatal intensive care unit admission, and intubation. Surfactant for respiratory distress syndrome was required by five infants, and five demonstrated persistent pulmonary hypertension of the newborn, which required high-frequency oscillation ventilation and inhaled nitric oxide administration. Inotropic support with or without hydrocortisone was required by four infants with haemodynamic instability (poor cardiac

TABLE 1. Characteristics of parents of patients with haemoglobin Bart's hydrops fetalis and reasons for continuation of pregnancy

Case	Ethnicity of parents	Gravidity (G) / parity (P) / abortion (A)	Maternal age at conception, y	Reason for continuation of pregnancy
1 <sup>14</sup>	Chinese	G3P2A1 *	24	No antenatal visit
2 <sup>6,13,15</sup>	Chinese	G3P2A1 †	36	Declined termination of pregnancy after counselling, for personal reasons
3 <sup>16,17</sup>	Chinese	G3P2A1	–	No antenatal visit because normal status given at antenatal examination in mainland China and this was first baby of second marriage
4	Chinese	G4P2A2 ‡	44	Declined termination of pregnancy for religious reasons
5 <sup>16</sup>	Chinese	G3P2	43	Pregnancy by in-vitro fertilisation; no antenatal visit because not entitled and told status was normal during private antenatal care
6 <sup>18,19</sup>	Chinese	G3P2	34	Parental choice to continue pregnancy after counselling
7	Chinese	G1P0	–	Antenatal screening was normal; possible non-paternity §
8	Chinese	G2P1	38	First child normal; opted for continuation of pregnancy for religious reasons
9	Chinese	G2P1	39	First child normal; parental choice to continue pregnancy after counselling

\* Divorced mother with a 6-year-old child with  $\alpha$ -thalassaemia trait and previous abortion at 20 weeks of gestation because of chickenpox infection; biological father was major carer since loss of contact with mother

† Couple with known  $\alpha$ -thalassaemia trait

‡ One stillbirth at 32 weeks of gestation in mainland China 13 years previously; one healthy baby boy delivered vaginally at term with birthweight 2.9 kg in Hong Kong 12 years previously; one surgical termination of pregnancy at first trimester in mainland China 7 years previously

§ Mother gave birth to a healthy baby 1 year later with different biological father; conceived again 2 years later (presumed same biological father as index case) but resulted in intrauterine death in first trimester because of haemoglobin Bart's hydrops fetalis

TABLE 2. Family history, antenatal features, and genetic characteristics of survival cases of haemoglobin Bart's hydrops fetalis

Case	Known family history	Availability of antenatal care	Antenatal screening/ ultrasonography findings	Antenatal complications	Means of diagnosis	Genotype of patient	Genotype of parents
1 <sup>14</sup>	Yes, couple known to be $\alpha$ -thalassaemia carriers	No	Not applicable	Preterm delivery at 24 wk by date, 30-32 wk by assessment	Haemoglobin pattern at birth *	--SEA/--SEA	Genetic study not done
2 <sup>6,13,15</sup>	Yes, couple known to be $\alpha$ -thalassaemia carriers	Yes	Hydropic with scalp oedema, ascites, and cardiomegaly at 22-wk USG	Preterm delivery at 29 wk for preterm labour	Cordocentesis †	--SEA/--SEA	Heterozygous SEA deletion in both parents
3 <sup>16,17</sup>	No, husband's MCV normal	Yes, in mainland China	Claimed normal in mainland China	Preterm delivery at 29 wk Maternal gestational hypertension on labetalol	Haemoglobin pattern at birth	--SEA/--SEA	Genetic study not done
4	Yes, couple known to be $\alpha$ -thalassaemia carriers	Yes	Cardiomegaly (CTR, 0.56), ‡ placentomegaly (2.8 cm), high MCA-PSV § (49 cm/s, >1.55 MoM), no hydrops, resolved pericardial effusion	None; delivered at 38 wk	Amniocentesis (19 wk)	--SEA/--SEA	Heterozygous SEA deletion in both parents
5 <sup>16</sup>	Yes, couple known to be $\alpha$ -thalassaemia carriers	Yes, private obstetrician	Amniotic fluid at 20 weeks: normal karyotype 46XY; 4D USG 20+5 wk: normal, liquor normal; 4D USG 28+3 wk: SGA <5th%; CTR >0.55, ambiguous genitalia, umbilical and fetal Doppler USG normal	Preterm delivery at 33 wk for fetal distress	Haemoglobin pattern at birth ¶	--SEA/--SEA	Heterozygous SEA deletion in both parents
6 <sup>18,19</sup>	Yes, mother with known $\alpha$ -thalassaemia trait but husband's MCV was normal	Yes	USG at 21 wk showed fetal hydrops with ascites, bilateral pleural effusions, cardiomegaly, and increased MCA-PSV (52.3 cm/s, >1.55 MoM)	Preterm delivery at 31 wk for fetal distress; given nifedipine for maternal gestational hypertension	Fetal CVS	--SEA/--SEA	Mother: heterozygous SEA deletion ( $\alpha$ -thalassaemia 1) Father: $\alpha$ 3.7 single deletion ( $\alpha$ -thalassaemia 2) Patient demonstrated maternal uniparental disomy and isodisomy
7	Yes, mother with known $\alpha$ -thalassaemia trait but husband's MCV was normal	Yes, private	Claimed to be normal	Preterm delivery at 33 wk for maternal chorionitis, MSL	Haemoglobin pattern at birth **	--SEA/--SEA	Mother refused genetic testing; possible non-paternity as revealed later from history given by mother
8	Yes, couple known to be $\alpha$ -thalassaemia carriers	Yes	Cardiomegaly (CTR, 0.55) and thickened placenta on USG at 16 wk of gestation	None; delivered at 38 wk	Fetal CVS (16 wk), cordocentesis (20 wk)	--SEA/--SEA	Heterozygous SEA deletion in both parents
9	Yes, couple known to be $\alpha$ -thalassaemia carriers	Yes	USG at 31+5 wk: placental thickness 3.8 cm; CTR, 0.63, MCA-PSV 71 cm/s; umbilical artery Doppler systolic/diastolic ratio 3.09, deepest pocket 6.29 cm	Preterm delivery at 32 wk, preterm premature rupture of membranes, MSL, acute funisitis	Cordocentesis	--SEA/--SEA	Heterozygous SEA deletion in both parents

Abbreviations: CTR = cardiothoracic ratio; CVS = chorionic villi sampling; Hb = haemoglobin; MCA-PSV = middle cerebral artery peak systolic velocity; MCV = mean corpuscular volume; MoM = multiple of the median; MSL = meconium stained liquor; SEA = Southeast Asian; SGA = small for gestational age; USG = ultrasonography

\* Hb Bart's 80.7%, Hb Portland 19.3%, complete absence of HbA, A2 and F, occasional HbH inclusion bodies

† Fetal Hb was 96 g/L with Hb Bart's 74% and Hb Portland 26%; the fetal karyotype was 46XY

‡ Assessment of mid-trimester CTR by USG assisted in the prenatal diagnosis of homozygous  $\alpha$ -thalassaemia with a CTR  $\geq$ 0.53 having sensitivity of 95.0% and specificity of 96.1% for prediction of affected pregnancies<sup>20</sup>

§ MCA-PSV is a useful, non-invasive tool for detection of fetal anaemia and hypoxia; value of >1.55 MoM for gestational age is considered clinically significant and an indication for intrauterine transfusion

|| Amniocentesis at 19 wk with DNA study showed absent  $\alpha$  gene, compatible with homozygous  $\alpha^0$ -thalassaemia

¶ Hb Bart's as major component with Hb Portland

\*\* Hb Bart's 85.8%, Hb Portland 14.2%, no HbA, HbF or HbA2 detected

contractility, heart failure, and/or hypotension). In case 6, the infant required cardiopulmonary resuscitation for more than 20 minutes after cardiac arrest. Postnatally, exchange transfusion was performed in five babies: two received a double-volume transfusion and three received a single-volume transfusion. Three infants received a transfusion within the first 24 hours of life. The median pre- and post-transfusion haemoglobin level was 90 and 170 g/L, respectively. All infants showed improved haemodynamic stability after transfusion. Congenital malformations were noted in all cases in this cohort (Tables 3 and 4).<sup>6,13-19</sup>

All four male babies had hypospadias that required urethroplasty, and two had concomitant undescended testes that required orchidopexy. Dental (case 1) and skeletal (case 3) anomalies were noted in two patients. Regarding the cardiovascular system, patent ductus arteriosus was noted in five cases and a secundum atrial septal defect in three. Regarding the digestive system, one infant (case 3) had type 3 jejunal atresia, for which end-to-end anastomosis was performed on day 4 of life. Two patients had neonatal hepatitis: one case resolved with time and the other still requires regular follow-up for elevated transaminase levels. No cases of cerebrovascular malformations were identified in this local cohort.

### Growth, puberty, and neurodevelopment

Both survivors who have reached adulthood are of short stature and have failed to achieve their final adult height, that is, to reach their predicted mid-parental height. Nonetheless, both had a normal puberty. Among the nine survivors, two have long-term neurological deficits, both manifested as mild spastic diplegia, although not affecting mobility. Five infants had delayed development, one of whom continues to have borderline low intellect (IQ, 80-89) after reaching adulthood (case 1). Two have normal intellect (cases 2 and 4) despite the need for multidisciplinary training during infancy, and the remaining two (cases 6 and 7) are attending mainstream schools that provide extra training and support. The two cases diagnosed most recently (cases 8 and 9) have had normal development to date (Tables 3 and 4).<sup>6,13-19</sup>

### Long-term outcomes and co-morbidities

Two patients received a stem-cell transplant: one an human leukocyte antigen DR 1 antigen-mismatch sibling-donor cord-blood transplant, and the other a 10/10 peripheral-blood stem-cell transplant from a matched unrelated donor. Both patients underwent transplantation at 20 to 21 months of age. Both achieved 100% donor chimerism 1 month after transplantation and remain transfusion-

independent. Of the remaining seven patients who require regular transfusion every 3 to 6 weeks, only one shows moderate hepatic iron overload (case 2), and none have demonstrated infective complications. All five survivors older than 2 years received iron chelation therapy: three with deferasirox and two with deferiprone (one of whom has changed to deferoxamine owing to neutropenia). The median serum ferritin level was 1961 pmol/L (range, 411-5312 pmol/L). Endocrinopathies were noted in three patients: one had primary gonadal failure but did not require hormonal replacement therapy (case 1), one had hypogonadism requiring testosterone (case 5), and one (case 2) had partial adrenal insufficiency requiring stress-dose steroid but not regular hydrocortisone replacement (Tables 4 and 5).<sup>6,13-19</sup>

## Discussion

In Southeast Asia, BHFS is the most common cause of fetal hydrops.<sup>5,21</sup> Because it is an autosomal recessive disorder, when both parents have two  $\alpha$ -globin gene deletions in cis on chromosome 16 (each parent,  $--/\alpha\alpha$ ), any offspring will have a 25% chance of having BHFS. In BHFS, haemoglobin tetramers of only gamma chains ( $\gamma_4$ ) is ineffective in erythropoiesis and oxygen delivery to tissues. The ensuing anaemia and tissue hypoxia interfere with organogenesis and development and also lead to fetal heart failure, extramedullary erythropoiesis, and maternal complications. In contrast to  $--^{FIL}$  and  $--^{THAI}$  gene deletions reported in the Philippines and Thailand, respectively, the  $--^{SEA}$  or Southeast Asian deletion (the most common mutation in Hong Kong and demonstrated in all nine BHFS cases in this study) affects only the  $\alpha$ -globin gene while sparing the embryonic  $\zeta$ -globin gene, thus permitting production of Portland 1 ( $\zeta_2\gamma_2$ ) and Portland 2 ( $\zeta_2\beta_2$ ) haemoglobins. Hence, the affected fetus can survive through the antenatal and early neonatal period.

### Pitfalls in prenatal screening and diagnosis

In Hong Kong, prenatal screening using a cut-off for maternal mean corpuscular volume of  $\leq 80$  fL and prenatal diagnosis using chorionic villus sampling, amniocentesis, and cordocentesis have been practised since 1983,<sup>22-25</sup> thereby contributing to a decline in BHFS incidence for two decades. Despite public health endeavours in prenatal screening, however, BHFS babies continue to be born without prior prenatal diagnosis or parental counselling, resulting in adverse maternal and fetal outcomes.<sup>26</sup> Causes of this phenomenon are principally two-fold: lack of proper antenatal screening and diagnosis, as well as improper implementation of screening or diagnostic procedures (Table 1). Better public education in both mainland China and Hong Kong would rectify

TABLE 3. Perinatal outcomes and morbidities in survival cases of haemoglobin Bart's hydrops fetalis

Case	Sex / Age	Delivery / birthweight / gestation / Apgar	IUT / IUET / ET	Neonatal course	
				Intubation and indication	Ventilation
1 <sup>14</sup>	F / 20 y	SVD / 1.00 kg (>97th %, LGA) / 24 wk / 2(1), 7(5)	–	Intubated shortly after birth for cyanosis	HFOV at birth then CPAP at 3 wk of life; mechanical ventilation for 2 mo total
2 <sup>6,13,15</sup>	M / 19 y	Emergency CS x preterm labour / 1.3 kg (50-75th %, AGA) / 29 wk / 4(1), 7(5)	IUET 3 times at 23, 25, 29 wk; no ET after birth	Intubated for RDS	IPPV for 6 d, mechanical ventilation for 11 d total
3 <sup>16,17</sup>	F / 10 y	– / 1.21 kg (<3rd %, SGA) / 35 wk / 4(1), 6(5)	No IUT, ET once	Intubated for PPHN and RDS	HFOV for 3 d; then extubated to CPAP on day 14
4	F / 8 y	Emergency CS x failed induction / 2.09 kg (<3rd %, SGA) / 37 wk / 5(1), 8(5)	IUT 2 times, double-volume ET once	Initially nasal CPAP, electively intubated as high O <sub>2</sub> requirement, unstable haemodynamics	Extubated on day 3
5 <sup>16</sup>	M / 7 y	Emergency CS x FD+BSL / 1.42 kg (5-10th %, SGA) / 33 wk / 3(1), 7(5)	No IUT, DVET once	Intubated in labour ward, born apnoeic and bradycardic	CPAP until day 17
6 <sup>18,19</sup>	F / 4 y	Emergency CS x FD / 1.36 kg (25-50th %, AGA) / 31 wk / 6(1), 7(5)	IUT 3 times, no ET	Intubated at birth, born depressed with SpO <sub>2</sub> 60% and bradycardia	HFOV initially then extubated on day 22, CPAP until day 26, remained O <sub>2</sub> -dependent until day 35
7	F / 4 y	AVBD / 1.94 kg (50th %, AGA), 33 wk / 5(1), 8(5)	No IUT or ET	Intubated at birth, born depressed with MAS and PPHN	HFOV, given inhaled NO until day 6, extubated to CPAP on day 15, then room air on day 17
8	M / 20 mo	SVD / 2.51 kg (3rd %, SGA) / 38 wk / 7(1), 8(5)	IUT 4 times at 20, 22, 27, 35 wk; single-volume ET once	Intubated in NICU for grunting, SpO <sub>2</sub> 60% on CPAP	SIMV for 3 d, then CPAP with steroid
9	M / 19 mo	SVD / 1.88 kg (50-75th %, AGA) / 32 wk / 4(1), 7(5)	IUT 3 times at 21, 27, 30 wk; single-volume ET once	Intubated in labour ward for respiratory depression and bradycardia	Intubated for 2 d then CPAP for 4 d followed by nasal cannula

Abbreviations: AGA = appropriate for gestational age; ASD = atrial septal defect; ATRX = alpha-thalassaemia mental retardation; AVBD = assisted vaginal breech delivery; BSL = blood-stained liquor; CPAP = continuous positive-pressure ventilation; CPR = cardiopulmonary resuscitation; Cr = creatinine; CS = caesarean section; DVET = double-volume exchange transfusion; ET = exchange transfusion (postnatal); F = female; FD = fetal distress; gestation = gestation (in weeks); HFOV = high-frequency oscillation ventilation; HIE = hypoxic-ischaemic encephalopathy; IPPV = intermittent positive-pressure ventilation; IUET = intrauterine exchange transfusion; IUT = intrauterine transfusion(s); IVH = intraventricular haemorrhage; LGA = large for gestational age; M = male; MAS = meconium aspiration syndrome; max = maximum; NEC = necrotising enterocolitis; NICU = neonatal intensive care unit; NO = nitric oxide; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PPHN = pulmonary hypertension of newborn; PT = phototherapy; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; SCBU = special care baby unit; SDH = subdural haemorrhage; SGA = small for gestational age; SIMV = synchronised intermittent mechanical ventilation; SpO<sub>2</sub> = oxygen saturation; SVD = spontaneous vaginal delivery; TPN = total parenteral nutrition; TPT = triple phototherapy; TR = tricuspid regurgitation; UDT = undescended testes

\* Urethroplasty and release of chordee done at 14 months of age. An episode of urinary tract infection due to *Klebsiella* at 18 months of age

† Urethroplasty and left orchidopexy performed at 15 months of age

Neonatal course		Congenital malformations		
Other complications	Length of stay	Urogenital anomalies	Skeletal / dental anomalies	Others
PPHN, HFOV, PDA 4 mm failed indomethacin on day 12 (renal impairment, thrombocytopenia and abdominal distension), ligated on day 19, tiny PFO, TPN for 37 d total, renal impairment with Cr max 176 µM, jaundice on day 2 needed PT for 1 d, no IVH/PVL, left grade 2 ROP, right grade 1 ROP	NICU 2 mo, SCBU 2 wk	None	Dental deformation, anodontia, malocclusion	None
Poor contractility with dilated and hypertrophic heart chambers requiring inotropic support, left grade 1 IVH, stage 3 zone 3 ROP	NICU 11 d, SCBU 2.5 mo	Glandular hypospadias, chordee	None	Moderate TR, mild mitral regurgitation, dysplastic tricuspid valve
PPHN requiring HFOV and NO, RDS needed surfactant 3 times, hypotension, max dopamine and dobutamine 30 µg/kg/min and hydrocortisone, weaned off inotropes on day 2, steroid on day 5	NICU 4 d in one hospital then 18 d in another, SCBU 68 d	None	Absence of all toes, shortened fingers	Type 3 jejunal atresia, hypertrophic cardiomyopathy
PPHN, PDA 5.6 mm, PFO 2 mm with heart failure, max dopamine 15 µg/kg/min and dobutamine 10 µg/kg/min, stopped all inotropes on day 5	NICU 8 d, SCBU 5 d	None	None	Small secundum ASD 2-3 mm
PDA 3.8 mm, closed with 5 doses of indomethacin, established full feeding on day 22, no sepsis or IVH	NICU 23 d, SCBU 32 d	Hypospadias, micropenis, bilateral UDT, hypoplastic scrotum	None	Male pseudo-hermaphrodite, suspected ATRX syndrome
Cardiac arrest, CPR with total of 8 doses of adrenaline and 3 doses of atropine given, HIE, grade III RDS, PPHN, bilateral stage 1-2 ROP resolved	NICU 28 d, SCBU 58 d, haematology ward for 20 d	None	None	ASD/PFO 5.7 mm, PDA 2.8 mm, dilated right atrium/ventricle and main pulmonary artery, severe TR
MAS, respiratory distress syndrome, given 3 doses of beractant, PPHN, HFOV, given NO, shock, severe jaundice, NEC	NICU 17 d, SCBU 45 d	None	None	Neonatal hepatitis syndrome
Congenital pneumonia, right-sided pneumothorax, TPN for 5 d total, no jaundice, bilateral grade 1 IVH resolved	NICU 7 d, SCBU 5 d	Proximal penile hypospadias *	None	PFO
RDS, given one dose of beractant, TPN for 16 d total, jaundice needed TPT, left grade 4 IVH and SDH, right grade 2 IVH resolved afterwards	NICU 26 d, SCBU 25 d	Penoscrotal hypospadias, dorsal hood, mild chordee, right hydrocoele, left UDT †	None	Fenestrated ASD, mild to moderate TR, PDA, heart failure, neonatal giant cell hepatitis

TABLE 4. Long-term outcomes and morbidities in survival cases of haemoglobin Bart's hydrops fetalis

Case	Sex / age	Growth	Neuro-development	Endocrinopathies
1 <sup>14</sup>	F / 20 y	FAH 152 cm (10th %), MPH 164 cm (50th %), BW 52 kg (50-75th %), BMI 22.6, normal insulin-like growth factor 1, delayed BA (4 y at CA 7 y) normalised	IQ 80-89, form 5 graduate, working in salon	Primary gonadal failure, USG of pelvis at age 17 y showed small ovaries; normal LH/FSH, low oestradiol, no need for hormone therapy; menarche at age 12 y, regular menses
2 <sup>6,13,15</sup>	M / 19 y	Short stature, FAH 154 cm (5 cm <3rd %), MPH 167 cm (25th %), BW 42 kg (<3rd %), normal BA (8 y at CA 8y)	Diploma student	Normal puberty, started at age 14 y, adrenal insufficiency, satisfactory baseline cortisol, stress-dose steroid
3 <sup>16,17</sup>	F / 10 y	Not available	Not available	Not available
4	F / 8 y	BH 116.5 cm (3rd %), MPH 151 cm (10th %), BW 23.7 kg (25-50th %), HC 49.5 cm (10-25th %)	GDD PBMT, GMDS score 23-31 mo at CA 37.5 mo, given PT/OT/ST, normalised, in mainstream school, USG and MRI of brain at 6 mo normal, mild tiptoe gait with bilateral lower limb spasticity	Prepubertal
5 <sup>16</sup>	M / 7 y	BH 120 cm (25th %), BW 24 kg (50th %)	Spastic diplegia, contrast MRI of brain at age 2 y normal	Prepubertal 46,XY disorder of sexual development, LH 3.7 IU/L, FSH 2.6 IU/L, testosterone 6.41, cortisol 155, USG of pelvis: no female genital organs, given testosterone ester blend 50 mg (Aug 2010, Jan 2011)
6 <sup>18,19</sup>	F / 5 y	BH 105.7 cm, (25-50th %), BW 17.1 kg (50th %)	At school	Prepubertal
7	F / 4 y	BH 93.3 cm (<3rd %), BW 12.8 kg (<3rd %)	At school with GDD	Prepubertal
8	M / 20 mo	HC 3rd-10th %, BH 78 cm (50th %), BW 9.7 kg (3rd-10th %)	Normal development	Prepubertal
9	M / 19 mo	HC 50th %, BH 78.3 cm (25th %), BW 10.8 kg (50th %)	Normal development	Prepubertal

Abbreviations: aGVHD = acute graft-versus-host-disease; BA = bone age; BH = body height (latest) [in cm]; BMI = body mass index; BW = body weight (latest); CA = chronological age; F = female; FAH = final adult height; FSH = follicle-stimulating hormone; GDD = global developmental delay; GMDS = Gross Motor Development Scale; HC = head circumference; IQ = intelligence quotient; LH = luteinising hormone; M = male; MPH = mid-parental height; MRI-T2\* = T2\*-weighted magnetic resonance imaging; OT = occupational therapy; PBMT = post-bone marrow transplantation; PT = physiotherapy; ST = speech therapy; UDT = undescended testis; USG = ultrasonography

the situation. Such education should stress the importance of early accurate prenatal diagnosis and the possible serious sequelae of late presentation or delayed diagnosis. Obstetricians should also note that normal paternal mean corpuscular volume does not exclude fetal BHFS because of the rare occurrence of maternal uniparental disomy (case 6)<sup>27</sup> and non-paternity (possible in case 7).<sup>27</sup> Routine

mid-trimester scanning is imperative and diagnosis of BHFS should be considered if ultrasonography or clinical features are suggestive of BHFS (cardiomegaly, placentomegaly,<sup>18,28</sup> and hydrops), regardless of the parents' mean corpuscular volume.<sup>27</sup> Placental thickness measurement allows early detection of BHFS in the first trimester, even before the appearance of hydropic features.<sup>18,28</sup> If



Dental and bone health	Transfusion, iron overloading, and related complications	Transplant-related complications	Others
Anodontia by age 12 y, dental caries, deformation, malocclusion, occasional back pain, no history of fracture, bone mineral density Z-score -3.7	Transfusion pre-transplant (every 4 wk), transfusion-independent post-transplant without major complications on 15-y long-term follow-up, good exercise tolerance with running and basketball	Cord-blood transplant from matched-sibling donor, human leukocyte antigen DR antigen mismatch, aGVHD and human herpesvirus 6 viraemia in 1998 (see Table 5 for more details)	Hyperuricaemia, hypertriglyceridaemia, transient alopecia areata at age 6-7 y resolved, eczema, hyperextended elbow joints but normal range of movement
None	Transfusion (every 4 wk), on deferoxamine (deferiprone was stopped for neutropenia), MRI-T2* at age 18 y: moderate liver iron overload (T2* 1.4-2.7 ms), no cardiac iron overload (T2* >20 ms)	Not applicable	Dysplastic tricuspid valve with incomplete coaptation and moderate tricuspid regurgitation
Absence of all toes, shortened fingers and syndactyly, separated with skin grafting at age 3 and 4 y, able to write (right hand dominance), closed reduction and fixation for traumatic right humeral supracondylar fracture at age 5 y	Transfusion (every 4 wk), on deferiprone, latest ferritin 1785 pmol/L	Not applicable	Type III jejunal atresia, end-to-end anastomosis on day 4 of life
Mild spastic diplegia affecting gastrocnemius, bilateral tight Achilles tendons, pes planus, calcaneovalgus	Transfusion-independent at 6 mo post-transplant, latest MRI T2* 4 y post-transplant: no pituitary / cardiac / hepatic / pancreatic iron overload, latest ferritin 411 pmol/L	Peripheral-blood stem-cell transplant from matched unrelated donor in Apr 2010, aGVHD of skin (grade 2) and gut (grade 3), human herpesvirus 7, stopped cyclosporine 14 mo post-transplant	Not applicable
None	Transfusion (every 3 wk), on deferasirox, latest ferritin 4167 pmol/L	Not applicable	Bilateral orchidopexy at 18 mo, Snodgrass procedure at age 3 y complicated by fistula and stricture, stenting for 2 mo, home dilatation for 6 mo, healed and normal urination, buried penis, loss of pubopenile angle
None	Transfusion (every 5 wk), on deferasirox since age 28 mo, latest ferritin 1961 pmol/L	Not applicable	Not applicable
None	Transfusion (every 4 wk), on deferasirox since age 2 y, latest ferritin 5312 pmol/L	Not applicable	Not applicable
None	Transfusion (every 4-6 wk)	Not applicable	Proximal penile hypospadias, urethroplasty and release of chordee at age 14 mo, episode of urinary tract infection due to <i>Klebsiella</i> at age 18 mo
None	Transfusion (every 4-5 wk)	Not applicable	Urethroplasty and left orchidopexy at age 15 mo for penoscrotal hypospadias and left UDT

hydropic changes are detected, confirmation by cordocentesis and haemoglobin electrophoresis is warranted.

### Counselling for parents in Hong Kong who opt to continue pregnancy

Suggested salient points of counselling for parents who opt for continuation of pregnancy are shown

in the online supplementary Appendix. Once considered fatal, BHFS can now be detected and diagnosed antenatally, with survival being possible albeit not without complications. Detailed antenatal counselling for parents who are contemplating continuation of an affected pregnancy is crucial. Possible maternal-fetal complications, such as gestational hypertensive disorder and intrauterine

TABLE 5. Stem-cell transplantation details and outcome for haemoglobin Bart's hydrops fetalis

Case	Donor	Stem-cell source	Transplant details	Conditioning regimen and prophylaxis	Early post-transplantation complications	Outcome
1 <sup>14</sup>	Mother homozygous for loci A and B (A2; B46; DRB1 08,09), pregnant 2 mo after birth of index child, no antenatal care until 20 wk, USG: no cardiomegaly, enlarged placenta, or hydrops; YB alpha-thalassaemia trait, HLA-DR 1 antigen mismatch (A 2,11; B 55,46; DRB1 04,08 in patient but 04,09 in donor)	From placenta of younger brother, cryopreserved without volume reduction  Cord blood volume 30 mL, total nucleated cell dose 4.8 x 10 <sup>7</sup> /kg, colony-forming units of granulocytes/monocytes 2.2 x 10 <sup>4</sup> /kg	Received cord-blood transplant from matched-sibling at age 20 mo (8 mo for younger brother)	Busulfan 5 mg/kg/d (days -9 to -6)  Cyclophosphamide 50 mg/kg/d (days -5 to -2)  Antithymocyte globulin 30 mg/kg/d (days -4 to -2)  Cyclosporin A (day -1), methotrexate (days +1, +3, +6, +11)	Fever on day 15; given amikacin, ceftazidime, vancomycin, sulperazone, foscarnet, amphotericin B  Polymerase chain reaction: serum human herpesvirus 6 +ve, skin tissue -ve; given foscarnet	Neutrophil engraftment on day +26, augmented with granulocyte colony-stimulating factor, platelet engraftment on day +38 (>20 x 10 <sup>9</sup> /L) and day +56 (>50 x 10 <sup>9</sup> /L)  Donor chimerism; 100% donor on day +29/30 and 30 mo post-transplant; transfusion dependency, last transfusion on day +30/32  Hb pattern: Hb 52.3% on day +69, declined gradually to 3.3% 9 mo later; Hb Bart's 10% 2 mo post-transplant, fell to undetectable level in 3 wk, Hb electrophoresis: globin chain synthesis $\alpha/\beta+\gamma$ ratio 0.86  Final outcome: converted to alpha-thalassaemia trait
4	Elder brother was healthy but not HLA-matched, mother had 16 eggs reserved for in-vitro fertilisation → pre-implantation genetic diagnosis for normal gamete selection → saved umbilical cord blood for hematopoietic stem-cell transplantation, 10/10 HLA-matched donor	Peripheral-blood stem cells, volume 40 mL  CD34 <sup>+</sup> cell dose 5.9 x 10 <sup>6</sup> /kg	Peripheral-blood stem-cell transplant from matched unrelated donor at age 21 mo	Busulfan 16 mg/kg, cyclophosphamide 200 mg/kg, antithymocyte globulin (horse) 90 mg/kg  Cyclosporin, methotrexate	Day +7, piperacillin/tazobactam → ticarcillin-clavulanate (stool grew Acinetobacter) → meropenem (persistent fever)  Day +13 vancomycin for methicillin-resistant coagulase-negative staphylococci; fever down but spike on day +25 → meropenem  Polymerase chain reaction: human herpesvirus 7 +ve on day +9, no transmission, -ve on day +31  Hepatosplenomegaly, liver 2 cm, spleen tip, abdominal distension and fluid retention; ultrasonography of abdomen normal, no hepatic veno-occlusive disease; chest X-ray on day +20: right pleural effusion, echo normal; pleural effusion resolved on day +25	Neutrophil engraftment on day +15  Platelet engraftment on day +17 (>20 x 10 <sup>9</sup> /L) and day +25 (>50 x 10 <sup>9</sup> /L)  Donor chimerism: 100% at 1 mo  Hb pattern: HbH bodies 20%

Abbreviations: Hb = haemoglobin; HLA = human leukocyte antigen; USG = ultrasonography

growth restriction or death, should be addressed. On the basis of local experience, IUT is advised because there is a risk of miscarriage or intrauterine infection (case 9). Multiple IUTs may be indicated if fetal anaemia is suggested by serial Doppler ultrasonography (peak systolic velocity of the middle

cerebral artery of >1.5 multiples of the median). Premature delivery and perinatal respiratory depression are often encountered. Neonatal intensive care unit admission and intubation are anticipated from local experience. Inotropic support may be required in the early neonatal period, as well

as cardiopulmonary support, such as mechanical ventilation, surfactant treatment, high frequency oscillation ventilation, and nitric oxide inhalation for persistent pulmonary hypertension of the newborn. Exchange transfusion is often performed postnatally, in most cases within the first 24 hours of life.

Congenital malformations are often encountered, the most common being genitourinary and musculoskeletal defects, but are usually amenable to surgical correction. It is worth noting that all male babies in our local cohort displayed hypospadias. Two-thirds of our patient cohort showed growth retardation, global developmental delay, and/or long-term residual neurological deficits. These findings are comparable to those from an international case series<sup>29</sup> and an overseas case report.<sup>11</sup> Lifelong hypertransfusions every 4 to 6 weeks and iron chelation are expected for BHFS survivors. Haematopoietic stem-cell transplantation is a possible cure and has been successful in some local cases (Table 3). Nevertheless, transplant-related mortality and morbidity should not be overlooked. The proposal that parents produce a subsequent sibling to serve as a 'saviour baby' and potential donor is feasible but raises ethical concerns. Careful consideration and proper parental counselling are necessary.

### Comparison of outcomes and morbidities between local and international cohorts

Globally, 69 survivors are reported in the international BHFS registry<sup>29</sup> with our local cohort (n = 9) contributing about one-seventh of cases. Approximately two-thirds of all cases used IUT<sup>29</sup> (41/69; 59%), which is similar to the proportion of local cases (5/9; 56%). Globally<sup>29</sup> and locally, most infants were delivered prematurely (respectively, 47/66; 71% and 7/9; 78%). Approximately one-fifth (14/69) of all BHFS survivors underwent stem-cell transplantation,<sup>29</sup> again similar to our local situation (2/9). Congenital anomalies were present in all of the local patients, compared with two-thirds (37/55; 64%) worldwide,<sup>29</sup> although urogenital and limb defects remained the most common. Nearly half (26/55; 47%) of global BHFS survivors demonstrated various degrees of transient or permanent neurodevelopmental impairment,<sup>29</sup> in contrast to two-thirds of our cohort. Sohan et al (2002)<sup>30</sup> described the first BHFS survivor in the United Kingdom: a 38-week-old baby girl of Hong Kong parents, who was referred at 21 weeks of gestation for hydrops fetalis, received serial IUT and had BHFS antenatally diagnosed. Two exchange transfusions were performed postnatally and the baby was discharged on day 6 of life followed by transfusions every 4 to 5 weeks. At the time of that publication, she was 18 months old and had normal growth and development apart from bilateral transverse palmar

creases and a mild lobster-claw deformity of the right foot.<sup>30</sup>

### Strengths, limitations, and recommendations

This is the first territory-wide multicentre retrospective study to describe in depth the basic demographic characteristics and perinatal and long-term outcomes of BHFS survivors in Hong Kong over the past two decades or so. It also explores the reasons and cultural circumstances for which parents opted to continue the pregnancy despite public health endeavours to promote antenatal screening. Furthermore, it adds two more local cases to those submitted and recently published by the BHFS International Consortium.<sup>29</sup> However, the small sample size precludes statistical analyses, and the data covers only the eight local public hospitals with haematology units and a period of 20 years (as the cut-off age in Hong Kong for paediatric care is 20 years and the Clinical Data Analysis and Reporting System began only in 1996). Survivors beyond 20 years of age and patients who defaulted follow-up to receive long-term medical care in the private sector or overseas were excluded from this study. In addition, the numbers of abortions and stillbirths, as well as BHFS babies with early neonatal death were not studied. Multidisciplinary collaboration between obstetricians, paediatric haematologists, and adult-care physicians at all local hospitals and concerted efforts in data collection and analysis are recommended. With the establishment of the Hong Kong Children's Hospital in 2018, it is hoped that a standardised protocol of management and counselling can be compiled, data collection streamlined, and analysis facilitated for future research.

To conclude, survival of patients with BHFS is possible but not without short- and long-term complications. Local epidemiology of BHFS survivors is similar to that reported for an international registry. Detailed antenatal counselling of parents with a non-judgemental attitude and cautious optimism are imperative.

### Supplementary information

Online supplementary information (Appendix) is available for this article at [www.hkmj.org](http://www.hkmj.org).

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The authors have no conflicts of interest to disclose.

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