HONG KONG MEDICAL JOURNAL 香港醫學雜誌

SUPPLEMENTARY INFORMATION

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to:

Wilson YK Chan, Alex WK Leung, CW Luk, Rever CH Li, Alvin SC Ling, SY Ha. Outcomes and morbidities of patients who survive haemoglobin Bart's hydrops fetalis syndrome: 20-year retrospective review. Hong Kong Med J 2018;24:Epub. Published online 6 April 2018. DOI: 10.12809/hkmj176336

Appendix. Suggested salient points of counselling for parents who opt for continuation of pregnancy (pages 1-2)

APPENDIX. Suggested salient points of counselling for parents who opt for continuation of pregnancy

1. Maternal-fetal complications

- Mothers who conceive a haemoglobin Bart's hydrops fetalis syndrome (BHFS) fetus are considered to have a high-risk pregnancy, almost always associated with varying degrees of obstetric complications such as gestational hypertensive disorder (60%), severe pre-eclampsia (30%), eclampsia, peripartum haemorrhage (11%), placenta praevia, abruptio placentae, retained placenta, renal failure, congestive heart failure, premature labour,[1-3] and shoulder dystocia, with the majority of complications occurring during the third trimester.[1,4]
- Maternal mortality rate can approach 50% for women with a hydropic fetus if not receiving adequate medical care.[3,5]
- Intrauterine growth restriction, intrauterine death, polyhydramnios or oligohydramnios, stillbirth, neonatal death, and long-term neonatal co-morbidities are common.[5]

2. Intrauterine interventions

- Intrauterine interventions reverse adverse maternal-fetal outcomes. So far, three modalities are available worldwide: namely, intrauterine transfusion (IUT) in aliquots (10-20 mL/kg estimated fetal weight), intrauterine exchange transfusion (IUET) and intrauterine hematopoietic stem-cell transplantation (HSCT).
- Despite reports that some BHFS fetuses who are not transfused in utero are born alive without hydropic features[6] for unexplained reasons (probably related to persistent expression of embryonic ξ-globin),[3,7] IUT theoretically alleviates prenatal anaemia, hypoxaemia and tissue hypoxia, promotes tissue oxygen delivery, reverses hydropic changes and prolongs pregnancy course, thus reducing chance of early fetal death, and maximising chance of survival,[8] as well as presumably improving birthweight and Apgar score, and shortening duration of mechanical ventilation.
- A local literature review in 2007[6] comparing outcomes of 26 BHFS survivors with or without prior IUT also showed that fetuses who received IUT had milder manifestations, less stormy neonatal course, and no major neurological deficits. Thus, IUT/IUET were performed for all 5 BFHS fetuses diagnosed antenatally in Hong Kong public obstetric units,[9] although a risk of miscarriage or intrauterine infection (case 9) existed. Currently, there is no local experience of IU HSCT.

3. Neonatal outcome

- Premature delivery and perinatal respiratory depression are often encountered. Neonatal intensive care unit admission and intubation are anticipated from local experience. Cardiopulmonary support in the early neonatal period such as mechanical ventilation, surfactant treatment, high-frequency oscillatory ventilation, and nitric oxide inhalation for persistent pulmonary hypertension of newborns, as well as inotropic support, may be required.
- Exchange transfusion is often performed postnatally, most often within the first 24 hours of life.

4. Congenital malformations

- At least 17% of BHFS newborns have at least one congenital anomaly, as fetal hypoxia disturbs organogenesis and development.[3,10-13]
- The genitourinary system is the most commonly affected system,[10,14] with hypospadias being most frequently encountered, as confirmed in our cohort.
- Musculoskeletal defects are also common (8%), as normal limb development occurs at 6 weeks of gestation.[3,10-12] One of our patients (11%) demonstrated absence of all toes and shortened fingers.
- Cardiac defects such as secundum atrial septal defect and patent ductus arteriosus are also frequently seen.
- Other anomalies reported in the literature include microcephaly, hydrocephaly, neuronal migrational defect, and hypoplasia of the lungs but were not seen in our cohort.

5. Long-term growth and development

- Growth retardation and global developmental delay were common in our patient cohort, as echoed by an international case series[15] and an overseas case report.[16]

APPENDIX. cont'd

6. Endocrinopathies and bone health
• Endocrinopathies in BHFS survivors are expected to be similar to those reported in β-thalassaemia major patients,[17] and include growth hormone deficiency, delayed puberty, diabetes mellitus, and hypothyroidism. A longer period of observation is warranted to look for these complications in BHFS. • Decreased bone density due to marrow expansion, chronic haemolysis, chronic anaemia, and iron toxicity is also reported in the literature[18] and is advised to be incorporated as part of the long-term follow-up assessment of BHFS survivors.
7. Curative therapies
• HSCT provides a possible chance of cure but depends on the availability of donor and resources. It may not provide long-term benefits to growth and development. HSCT may have significant morbidity and mortality, such as veno-occlusive disease, acute and chronic graft versus host disease, post-transplant lymphoproliferative disease, and idiopathic interstitial pneumonitis. • To date, only 2 of 9 patients underwent HSCT postnatally and were successful (see Table 3). Careful consideration and proper counselling are necessary. Currently, there is no territory-wide unified protocol on optimal timing, donor source, stem-cell type or conditioning regimen. • The proposal of having a saviour baby as a potential donor raises ethical concerns.

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