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# Fetal Anemia in Northern Thailand: Etiologies and Outcomes

**Chitsanupong Ratarat[1], Rungrote Natesirinilkul[1,2], Lalita Sathitsamitphong[1,2], Chane Choed-Amphai[1,2], Kanda Fanhchaksai[1,2], Pimlak Charoenkwan[1,2] and Theera Tongsong[2,3]**

*[1]Department of Pediatrics, [2]Thalassemia and Hematology Center, [3]Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Correspondence:
Pimlak Charoenkwan, MD,
Department of Paediatrics,
Faculty of Medicine, Chiang Mai University, 110 Inthawarorot Rd, Sri Phum Subdistrict Mueang Chiang Mai District, Chiang Mai 50200, Thailand.
E-mail: pimlak.c@cmu.ac.th

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## ABSTRACT

**OBJECTIVE** In Southeast Asia, hemoglobin (Hb) Bart's disease is the primary cause of fetal anemia, although other causes are increasingly being identified. This study aimed to characterize the etiologies and outcomes of fetal anemia in northern Thailand.

**METHODS** A retrospective chart review was conducted, involving pregnant women who attended antenatal care at Chiang Mai University Hospital between 2014 and 2021 and had a diagnosis by ultrasound findings of fetal anemia, or a fetal diagnosis of Hb Bart's disease or other known hereditary anemias.

**RESULTS** Among 71 fetuses from 64 pregnancies, 45 (63.4%) had Hb Bart's disease. Twelve cases (16.9%) of fetal anemia were from other causes, including three cases of homozygous Hb Constant Spring, three cases of hereditary pyropoikilocytosis, one case of suspected red cell membrane disorder, one case each of Rh(D) alloimmunization, Hb H/Hb Pakse disease, transient abnormal myelopoiesis, syphilis infection, and one of unknown cause. All of the seven sets of twins (19.7%) had twin-to-twin transfusion syndrome (TTTS). Intrauterine transfusion was given in four cases of fetal hemolytic anemia which rendered good outcomes. Overall, 12 cases (16.9%) survived beyond the neonatal period.

**CONCLUSIONS** Hb Bart's disease remains the leading cause of fetal anemia in northern Thailand. Increasingly, frequently diagnosed causes include hemoglobinopathies and red cell membrane disorders.

**KEYWORDS** fetal anemia, Hb Bart's disease, Hb Constant Spring, hydrops fetalis, red cell membrane disorders

## INTRODUCTION

Fetal anemia is a significant complication in fetuses. Untreated fetal anemia can lead to hydrops fetalis and fetal demise. Clinical presentations of fetal anemia include fluid collection in the third space, decreased fetal activity, cardiomegaly, hepatosplenomegaly, and an enlarged placenta. Hydrops fetalis commonly develops in advanced cases, characterized by fluid collection in at least two body compartments, and is associated with a high perinatal mortality rate of 50-98% (1, 2).

The etiologies of fetal anemia can be categorized into two groups: immune-mediated and non-immune mediated causes. Rh(D) alloimmunization is the primary cause of immune-mediated fetal anemia in Western populations (3). The use of intravenous anti-Rh(D) immunoglobulin (anti-D Ig) prophylaxis has reduced the incidence of hemolytic disease of the fetus and newborn (HDFN) due to Rh(D) alloimmunization (4). In Southeast Asian populations, Rh(D) alloimmunization is less common due to the low prevalence of the Rh(D)-

negative blood group (1.7%) compared with that in Western populations (17.3%) (5). The leading cause of fetal anemia among Asian populations is hemoglobin (Hb) Bart's disease resulting from homozygous alpha$^0$-thalassemia (2, 6-8).

In a previous study conducted over a 10-year period in central Thailand, 78 cases of fetal hydrops in stillborns were examined, revealing anemia as the predominant cause (42% of cases), with half of the cases attributed to homozygous alpha$^0$-thalassemia (9). A recent study of alpha-thalassemia mutations in Southeast Asia, including Thailand, demonstrated a high burden of alpha-thalassemia in Thailand (10). In 2020, 423 new cases of Hb Bart's hydrops fetalis were estimated to have occurred in the country, with the highest absolute burden observed in Bangkok (the capital city) and Udon Thani (a province in the northeastern region). Chiang Mai, the largest city in northern Thailand, also displayed a high prevalence of alpha$^0$-thalassemia (10). Two large case series conducted in Thailand have consistently identified homozygous alpha$^0$-thalassemia as the leading cause of hydrops fetalis. Other causes of fetal anemia include homozygous Hb Constant Spring (CS), cardiovascular abnormalities, infections, and red cell membrane disorders (7, 9, 11-13).

Thailand has successfully established a prenatal screening and diagnosis program for couples at risk of severe thalassemia diseases (14). This program offers genetic counseling, prenatal screening, and prenatal diagnosis for couples at risk of having a fetus with severe thalassemia. In cases of homozygous alpha$^0$-thalassemia, termination of pregnancy is offered to prevent adverse maternal outcomes. The implementation of this program has resulted in a decrease in the number of undetected cases of fetal anemia.

The aim of this study is to examine the causes, treatment strategies, and outcomes of fetal anemia at Chiang Mai University Hospital, a tertiary care hospital in northern Thailand. The results may provide insights into the various diseases that contribute to the occurrence of fetal anemia in the region.

## METHODS

A retrospective descriptive study was conducted with the ethical approval of the Institutional Review Board, Faculty of Medicine, Chiang Mai University (Research study ID: PED-2562-06931). The full medical records, including clinical and laboratory information of pregnancies with fetal anemia and/or hydrops fetalis associated with anemia, of patients who were treated at Chiang Mai University Hospital from 2014 through 2021 were comprehensively reviewed. The review process included two steps as follows: First, we screened and retrieved medical records from the hospital for diagnoses potentially associated with fetal anemia and/or hydrops fetalis, including ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10$^{th}$ Revision) codes O361-363, P50, P55, P56, P613, P614, and P832. After that, the confirmed cases were reviewed in detail.

Fetal anemia was defined based on one or more of the following criteria: ultrasound findings of middle cerebral artery-peak systolic velocity (MCA-PSV) greater than 1.5 MoM, other ultrasound findings indicating fetal anemia, fetal hematocrit levels below 30%, and fetal diagnosis through Hb analysis or molecular methods indicating homozygous alpha$^0$-thalassemia (14). Hydrops fetalis was defined as the presence of excessive fluid accumulation in two or more body cavities. Demographic, clinical, and laboratory data of the mothers, fetuses and newborns were validated, recorded and analyzed.

Frequencies are presented as numbers and percentages. Continuous data is presented as medians plus interquartile range (IQR) or mean ± standard deviation, according to the normality of the data distribution. Statistical analysis was performed using SPSS Statistics for Windows, (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA, IBM Corp.).

## RESULTS

A total of 1,755 medical records were retrieved and screened, revealing 71 fetuses from 64 pregnancies diagnosed with fetal anemia and/or hydrops fetalis associated with anemia. Table 1 presents the clinical characteristics, etiologies, and outcomes of these cases. Of all the cases, 57 (80.3%) were diagnosed with fetal anemia, and 14 (19.7%) had fetal anemia/volume overload from twin-to-twin transfusion syndrome (TTTS). Table 2 provides the clinical characteristics and outcomes categorized by etiology.

**Table 1.** Clinical characteristics, etiologies, and outcomes of 64 pregnancies (71 fetuses) with a diagnosis of fetal anemia

| Clinical characteristics | Results |
|---|---|
| Maternal age (median, IQR, year) | 28.5 (11.0) |
| Gestational age at diagnosis (median, IQR, week) | 20 (7) |
| Gestational age at delivery (median, IQR, week) | 21 (9) |
| Birth weight (median, IQR, g) | 450 (895) |
| Diagnosis | |
| Fetal anemia (N, %) | |
| - Hb Bart's disease (homozygous alpha0-thalassemia) | 45 (63.4%) |
| - Hemolytic anemia | 9 (12.7%) |
| - Syphilis infection | 1 (1.4%) |
| - Transient abnormal myelopoiesis | 1 (1.4%) |
| - Anemia, unknown cause | 1 (1.4%) |
| Fetal anemia/volume overload (N, %) | |
| - Twin-twin transfusion syndrome | 14 (19.7%) |
| Outcomes (N, %) | |
| - Termination of pregnancy | 48 (67.6%) |
| - Fetal demise *in-utero* | 8 (11.3%) |
| - Neonatal death | 3 (4.2%) |
| - Survival beyond neonatal period | 12 (16.9%) |

**Table 2.** Clinical characteristics and outcomes of 64 pregnancies (71 fetuses) with a diagnosis of fetal anemia as classified by etiology

| Clinical characteristics | Fetal anemia | | | | | Fetal anemia/ volume overload |
|---|---|---|---|---|---|---|
| | Hb Bart's disease (N = 45) | Hemolytic anemia (N = 9) | Syphilis infection (N = 1) | Anemia (unknown cause) (N = 1) | Transient abnormal myelopoiesis (N = 1) | Twin-twin transfusion syndrome (N = 14) |
| Maternal age (median, IQR, year) | 31 (9) | 23 (14) | 23 | 22 | 40 | 29 (7) |
| Gestational age at diagnosis (median, IQR, week) | 18 (9) | 24.5 (11) | 23 | 22 | 25 | 25 (6) |
| Gestational age at delivery (median, IQR, week) | 20 (7) | 33 (11) | 23 | 26 | 33 | 27.5 (8) |
| Birth weight (median, IQR, g) | 300 (415) | 1,833 (1,781) | 875 | NA | 1,985 | 1,145 (1,141) |
| Treatment with intrauterine transfusion (N, %) | - | 4 (44.4%) | - | - | - | - |
| Outcomes (N, %) | | | | | | |
| - Termination of pregnancy | 45 (100%) | 1 (11.1%) | - | - | - | 2 (14.3%) |
| - Fetal demise inutero | - | 1 (11.1%) | 1 (100%) | 1 (100%) | - | 5 (35.7%) |
| - Neonatal death | - | 1 (11.1%) | - | - | 1 (100%) | 1 (7.1%) |
| - Survival beyond neonatal period | - | 6 (66.7%) | - | - | - | 6 (42.9%) |

### Hb Bart's disease

The most common cause identified was Hb Bart's disease resulting from homozygous Southeast Asian deletional alpha$^0$-thalassemia, accounting for 63.4% (45 out of 71 cases). Of those, 42 were diagnosed through the prenatal screening and diagnosis program, whereas the remaining three cases with incomplete screening were detected by prenatal sonographic signs of fetal anemia in the second trimester. Among the 45 pregnancies, 32 couples opted for prenatal diagnostic techniques such as chorionic villi sampling,

amniocentesis, or cordocentesis to confirm the diagnosis of Hb Bart's disease. Thirteen couples chose serial ultrasound monitoring, all of which developed hydropic changes, leading to invasive prenatal diagnosis for confirmation. Common ultrasound findings in this group included cardiomegaly (53.3%), high MCA-PSV (44.4%), and pericardial effusion (28.9%). The median (IQR) gestational age at diagnosis was 16 (6.5) weeks for the prenatal diagnostic test group and 22 (4.5) weeks for the serial ultrasound group. After counseling, all pregnancies affected by Hb Bart's disease were terminated.

**Hemolytic anemias other than Hb Bart's disease**

Nine fetuses were diagnosed with hemolytic anemia other than Hb Bart's disease, including three cases of homozygous Hb CS, three cases of hereditary pyropoikilocytosis (HPP) caused by homozygous or compound heterozygous *SPTB* or *SPTA1* mutations as identified by whole exome sequencing analysis (11), and 1 case each of Hb H/Hb Pakse disease, unidentified red cell membrane disorder, and Rh(D) alloimmunization. The diagnosis of unidentified red cell membrane disorder in one fetus was made based on findings of abnormal red cell morphology in the fetus and the parents; molecular analysis was not performed in this family. All fetuses exhibited signs of anemia and/or hydrops fetalis in the second or third trimesters. Common ultrasound findings in this group were cardiomegaly (66.7%), high MCA-PSV (55.6%), pericardial effusion (55.6%), and ascites (44.4%). One fetus diagnosed with HPP was terminated, while one fetus with an unidentified red cell membrane disorder died in utero. One fetus with HPP died during the neonatal period. Intrauterine transfusion was administered to four fetuses: one with Rh(D) alloimmunization, one with Hb H/Hb Pakse disease, and two with homozygous Hb CS. One fetus with homozygous Hb CS and fetal anemia did not receive intrauterine transfusion due to a parental decision against invasive prenatal interventions. Ultrasonographic evaluation at 21 weeks of gestational age revealed high MCA-PSV and fetal cardiomegaly. Regular monitoring with ultrasonography demonstrated resolution of anemia signs by 32 weeks of gestation. The patient was delivered at 39 weeks of gestation. He had congenital pneumonia necessitating mechanical ventilation for a period of two days. At birth, hemoglobin and hematocrit levels were measured at 13.9 g/dL and 44.3%, respectively, with no requirement for red blood cell transfusion during the neonatal period.

The patient group with hemolytic anemias other than Hb Bart's disease had the highest perinatal survival rate (66.7%), with 6 surviving fetuses. Among the survivors, only the one case with HPP remained transfusion-dependent. Despite receiving intrauterine transfusion and anti-D immunoglobulin, the newborn with Rh(D) alloimmunization experienced perinatal complications of severe hemolysis requiring partial exchange transfusion and jaundice from inspissated bile syndrome. Three newborns with homozygous Hb CS and one with Hb H/Hb Pakse disease survived beyond the neonatal period. Table 3 shows the clinical characteristics and treatment received during neonatal period of the six surviving fetuses in this group.

**Anemia from other causes**

In the fetal anemia group, apart from hemolytic anemia, there was one fetus with trisomy 21 and transient abnormal myelopoiesis (TAM) who died during the neonatal period, one fetus with syphilis infection, and one with a condition of unknown cause. The latter two fetuses died in utero.

**Twin-to-twin transfusion syndrome (TTTS)**

TTTS was observed in 14 fetuses of 7 pregnancies. Initial ultrasound findings included ascites (50.0%), generalized skin edema (42.8%), cardiomegaly (35.7%), and pericardial effusion (28.6%). TTTS was diagnosed in the second or third trimesters. None received laser coagulation. This group had the second highest perinatal survival rate (42.9%).

## DISCUSSION

Hb Bart's disease or homozygous alpha$^0$-thalassemia remains the most prevalent cause of fetal anemia in northern Thailand, indicating a high gene frequency of alpha$^0$-thalassemia in the population. The leading diagnosis of Hb Bart's disease in our study is consistent with that reported in previous studies in Thailand and China (2, 7, 13, 15). Increasingly, diagnosed causes of fetal anemia are non-deletional alpha-thalassemia and hereditary

**Table 3.** Clinical characteristics and treatment received during neonatal period of six surviving fetuses in the group of hemolytic anemias other than Hb Bart's disease

| Case number | Diagnosis | GA at onset of anemia | GA at delivery | Birth weight (g) | Intrauterine transfusion (times) | Hb before IUT (g/dL) | Hb at birth (g/dL) | Treatment received during neonatal period |
|---|---|---|---|---|---|---|---|---|
| 1 | Rh alloimmunization | 32 | 34 | 2,210 | 1 | 4.2 | 6.1 | Red cell transfusion<br>Phototherapy<br>Exchange transfusion |
| 2 | Hereditary pyropoikilocytosis | 30 | 30 | 1,455 | 0 | 3.6 | 4.5 | Red cell transfusion<br>Phototherapy<br>Exchange transfusion |
| 3 | Hb H/Hb Pakse disease | 18 | 37 | 2,860 | 1 | 6.5 | 17.2 | Phototherapy |
| 4 | Homozygous Hb Constant Spring | 21 | 39 | 2,805 | 0 | not done | 13.9 | Ventilator support for congenital pneumonia |
| 5 | Homozygous Hb Constant Spring | 25 | N/A | N/A | 1 | N/A | N/A | N/A |
| 6 | Homozygous Hb Constant Spring | 22 | 40 | 3,310 | 1 | 4.7 | 15.0 | Phototherapy |

*GA, gestational age; Hb, hemoglobin; IUT, intrauterine transfusion; N/A, data not available

red cell membrane disorders. Of note, only one fetal anemia associated with Rh(D) alloimmunization was identified in this study, suggesting a low prevalence of the Rh(D)-negative blood group in the Thai population.

Hb CS is a commonly observed Hb variant in Southeast Asian populations (16). Hb CS results from a nucleotide substitution at the termination codon of the alpha-2 globin gene, *HBA2*:c.427 T>C. This substitution replaces the termination codon with glutamine, resulting in an elongated and unstable alpha-globin variant (17). The compound heterozygosity of alpha$^0$-thalassemia and Hb CS results in Hb H/Hb CS disease, which typically presents with a moderate degree of chronic hemolytic anemia. Some patients may require regular transfusion for an extended period. In older children and adults with homozygous Hb CS, mild non-transfusion-dependent chronic hemolytic anemia is commonly observed. However, homozygous Hb CS has been reported as a cause of fetal anemia that shows a good response to treatment and a good long-term outcome (12, 18, 19). These fetuses may present with severe anemia necessitating intrauterine transfusion. Nevertheless, in late gestation, hemolysis tends to decrease, possibly because of Hb switching process, resulting in lower Hb F and higher Hb A levels. The anemia becomes milder after birth. Considering the potential impact of homozygous Hb CS, it is crucial to include it in the differential diagnosis of fetal anemia in Southeast Asian populations. Early diagnosis and intervention can contribute significantly to achieving a favorable outcome. In this study, fetuses with homozygous Hb CS and Hb H/Hb Pakse who received intrauterine transfusion were born at term with a normal Hb level and did not require red cell transfusion during the neonatal period.

Hb H disease results from mutations affecting three out of four functioning alpha-globin alleles, leaving one intact alpha-globin allele. Hb H disease can be classified as either deletional (genotype --/-α) or non-deletional (genotype --/α$^T$α or --/α α$^T$) Hb H disease. Generally, patients with Hb H disease present with a mild to moderate degree of anemia. Patients with non-deletional Hb H disease experience more severe anemia and may be transfusion dependent. Hb H hydrops fetalis represents the most severe form of Hb H disease, characterized by severe fetal anemia. Mutations causing Hb H hydrops fetalis typically involve alpha$^0$-thalassemia on one chromosome and a non-deletional mutation causing a hyperunstable or unstable Hb on the other chromosome (20, 21). Previously reported genotypes of common Hb H

disease that can be associated with Hb H hydrops fetalis are Hb H/Hb CS disease and Hb H/Hb Pakse diease (22, 23). One case in this study was diagnosed with Hb H/Hb Pakse disease.

Red cell membrane disorders are a frequently diagnosed cause of fetal severe hemolytic anemia (11, 24). The availability of next-generation sequencing has facilitated the identification of causative mutations and related genes. In this study, three cases of HPP were identified, indicating a high prevalence of HE in the population. Accurate molecular diagnosis of HPP is essential for treatment planning and genetic counseling.

TTTS is a potentially life-threatening complication that occurs in 10-15% of monochorionic twin pregnancies (25). This condition arises from an imbalance of blood flow between the placental anastomoses. Hydrops fetalis typically develops in the donor fetus due to anemia and high-output heart failure. Signs of heart failure include subcutaneous edema, ascites, and pericardial to pleural effusion prior to the development of hydrops fetalis (26, 27).

Diagnosis of TTTS is based on ultrasound findings (28). To facilitate early detection, it is recommended that biweekly ultrasounds be performed after 16 weeks of gestational age for monochorionic twins to evaluate fetal growth and amniotic fluid volume. MCA-PSV and umbilical artery flow pattern should be assessed after 20 weeks of gestational age (29). Fetoscopic laser coagulation is the standard treatment for TTTS between 17 and 26 weeks of gestational age and is intended to interrupt the anastomoses. This intervention leads to survival rates of approximately 70% for both twins and at least 90% for pregnancies with at least one survivor (30).

Of note, the compilation of the ICD-10 codes used in this study was designed to identify as many fetal anemia cases as possible. A total of 1,755 medical records were screened, but only 71 fetuses were enrolled. A large number of cases were excluded due to overlaps with diagnoses of other common conditions such as neonatal hyperbilirubinemia, non-anemic hydrops fetalis resulting from other causes and anemia with neonatal onset. Limitations of this study include the lack of long-term neurodevelopmental evaluation in perinatal survivors. Additionally, due to the retrospective nature of the study, some medical records may not have been entirely reliable, potentially resulting in under-diagnosis of fetal anemia and so may have been missed during the review.

## CONCLUSIONS

In conclusion, this study demonstrates that Hb Bart's disease remains the primary cause of fetal anemia in the northern Thai population. Homozygous Hb CS, Hb H hydrops fetalis, and red cell membrane disorders are increasingly diagnosed causes of fetal anemia. Intrauterine transfusion has been proven to be beneficial in cases of homozygous Hb CS.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

## REFERENCES

1. Takci S, Gharibzadeh M, Yurdakok M, Ozyuncu O, Korkmaz A, Akcoren Z, et al. Etiology and outcome of hydrops fetalis: report of 62 cases. Pediatr Neonatol. 2014;55:108-13.
2. He S, Wang L, Pan P, Wei H, Meng D, Du J, et al. Etiology and Perinatal Outcome of Nonimmune Hydrops Fetalis in Southern China. AJP Rep. 2017;7:e111-5. PubMed PMID: 28611934
3. McEwan A. Fetal anaemia. Obstet Gynaecol Reprod Med. 2015;25:22-8.
4. Mari G, Norton ME, Stone J, Berghella V, Sciscione AC, Tate D, Schenone MH, Society for Maternal-Fetal Medicine (SMFM) Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline# 8: the fetus at risk for anemia–diagnosis and management. Am J Obstet Gynecol. 2015;212:697-710.
5. Garratty G, Glynn SA, McEntire R, Retrovirus Epidemiology Donor S. ABO and Rh(D) phenotype frequencies of different racial/ ethnic groups in the United States. Transfusion. 2004;44:703-6.
6. Ng ZM, Seet MJ, Erng MN, Buendia F, Chang AS, Sriram B. Nonimmune hydrops fetalis in a children's hospital: a six-year series. Singapore Med J. 2013;54:487-90.

7. Ratanasiri T, Komwilaisak R, Sittivech A, Kleebkeaw P, Seejorn K. Incidence, causes and pregnancy outcomes of hydrops fetalis at Srinagarind Hospital, 1996-2005: a 10-year review. J Med Assoc Thai. 2009;92:594-9.
8. Thong XY, Lee LY, Chia DA, Wong YC, Biswas A. Management and Outcomes of Fetal Hydrops in a Tertiary Care Centre in Singapore. Ann Acad Med Singapore. 2017;46:4-10.
9. Taweevisit M, Thorner PS. Hydrops fetalis in the stillborn: a series from the central region of Thailand. Pediatr Dev Pathol. 2010;13:369-74.
10. Hockham C, Ekwattanakit S, Bhatt S, Penman BS, Gupta S, Viprakasit V, et al. Estimating the burden of α-thalassaemia in Thailand using a comprehensive prevalence database for Southeast Asia. eLife. 2019;8:e40580. PubMed PMID: 31120421
11. Ittiwut C, Natesirinilkul R, Tongprasert F, Sathitsamitphong L, Choed-Amphai C, Fanhchaksai K, et al. Novel mutations in SPTA1 and SPTB identified by whole exome sequencing in eight Thai families with hereditary pyropoikilocytosis presenting with severe fetal and neonatal anaemia. Br J Haematol. 2019;185:578-82.
12. Sirilert S, Charoenkwan P, Sirichotiyakul S, Tongprasert F, Srisupundit K, Luewan S, et al. Prenatal diagnosis and management of homozygous hemoglobin constant spring disease. J Perinatol. 2019;39:927-33.
13. Suwanrath-Kengpol C, Kor-anantakul O, Suntharasaj T, Leetanaporn R. Etiology and outcome of non-immune hydrops fetalis in southern Thailand. Gynecol Obstet Invest. 2005;59:134-7.
14. Tongsong T, Charoenkwan P, Sirivatanapa P, Wanapirak C, Piyamongkol W, Sirichotiyakul S, et al. Effectiveness of the model for prenatal control of severe thalassemia. Prenat Diagn. 2013;33:477-83.
15. Meng D, Li Q, Hu X, Wang L, Tan S, Su J, et al. Etiology and Outcome of non-immune Hydrops Fetalis in Southern China: report of 1004 cases. Sci Rep. 2019;9:10726. PubMed PMID: 31341179
16. Laig M, Pape M, Hundrieser J, Flatz G, Sanguansermsri T, Das BM, et al. The distribution of the Hb Constant Spring gene in Southeast Asian populations. Hum Genet. 1990;84:188-90.
17. Clegg JB, Weatherall DJ, Milner PF. Haemoglobin Constant Spring—A Chain Termination Mutant ? Nature. 1971;234:337-40.
18. Charoenkwan P, Sirichotiyakul S, Chanprapaph P, Tongprasert F, Taweephol R, Sae-Tung R, et al. Anemia and hydrops in a fetus with homozygous hemoglobin Constant Spring. J Pediatr Hematol Oncol. 2006;28:827-30.
19. He Y, Zhao Y, Lou J-W, Liu Y-H, Li D-Z. Fetal anemia and hydrops fetalis associated with homozygous Hb constant spring (HBA2: c.427T>C). Hemoglobin. 2016;40:97-101.
20. Lorey F, Charoenkwan P, Witkowska HE, Lafferty J, Patterson M, Eng B, et al. Hb H hydrops foetalis syndrome: a case report and review of literature. Br J Haematol. 2001;115:72-8.
21. Henderson S, Pitman M, McCarthy J, Molyneux A, Old J. Molecular prenatal diagnosis of Hb H Hydrops Fetalis caused by haemoglobin Adana and the implications to antenatal screening for α-thalassaemia. Prenat Diagn. 2008;28:859-61.
22. Luewan S, Charoenkwan P, Sirichotiyakul S, Tongsong T. Fetal haemoglobin H-Constant Spring disease: a role for intrauterine management. Br J Haematol. 2020;190:e233-6. PubMed PMID: 32488867.
23. Luewan S, Sirichotiyakul S, Charoenkwan P, Phirom K, Tongsong T. Hydrops Fetalis Associated with Fetal Hemoglobin H-Pakse Disease. Fetal Diagn Ther. 2022;49:528-35.
24. Songdej D, Kadegasem P, Tangbubpha N, Sasanakul W, Deelertthaweesap B, Chuansumrit A, et al. Whole-exome sequencing uncovered genetic diagnosis of severe inherited haemolytic anaemia: Correlation with clinical phenotypes. Br J Haematol. 2022;198:1051-64.
25. Hecher K, Gardiner HM, Diemert A, Bartmann P. Long-term outcomes for monochorionic twins after laser therapy in twin-to-twin transfusion syndrome. Lancet Child Adolesc Health. 2018;2:525-35.
26. Bliss JM, Carr SR, De Paepe ME, Luks FI. What—and Why—the Neonatologist Should Know About Twin-To-Twin Transfusion Syndrome. NeoReviews. 2017;18:e22-32.
27. Yoda H. Fetal and neonatal circulatory disorders in twin to twin transfusion syndrome (The secondary publication). J Nippon Med Sch. 2019;86:192-200.
28. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol. 1999;19:550-5.
29. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol. 2016;47:247-63.
30. Bamberg C, Hecher K. Twin-to-twin transfusion syndrome: Controversies in the diagnosis and management. Best Pract Res Clin Obstet Gynaecol. 2022;84:143-54.