# Beating the odds: A case report on the successful management of a non-immune hydrops fetalis due to hemoglobin Bart's disease*

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**ABSTRACT**

Hemoglobin Bart's hydrops fetalis, characterized by a deletion of all four α-globin genes is the most severe and lethal form of Thalassemia disease. Mortality rate usually ranges from 60-100% of cases.[1-5] Given the poor overall prognosis, most countries resort to pregnancy termination or expectant management as the only options to offer affected pregnancies.[5]

This paper presents a case of the successful management of a primigravid, diagnosed with hydrops fetalis at 29 4/7 weeks age of gestation. She delivered successfully to a live, preterm, baby boy who was later found out to have hydrops fetalis due to Hemoglobin Bart's disease, and currently, continues to thrive past eight months of age.

This report aims to improve the clinicians' knowledge regarding the work up and management of pregnant patients diagnosed with hydrops fetalis, and increase the clinician's awareness on the epidemiology, importance of targeted screening, and diagnosis of Alpha-Thalassemia in Filipino patients.

*Keywords: Alpha-Thalassemia, Hemoglobin Bart's, Hydrops Fetalis, Philippines*

## INTRODUCTION

Hydrops fetalis is a serious fetal condition characterized by abnormal accumulation of fluid in two or more fetal compartments, and may present as ascites, pericardial or pleural effusion, and skin edema.[5,6,8] Majority of cases, if not all, result to death in utero or mortality within hours after birth. Non-immune hydrops fetalis (NIHF), which refers specifically to cases not caused by Rh blood group incompatibility or other fetal-maternal incompatibility, accounts for 76 to 87% of all described cases of hydrops fetalis. In Southeast Asia, Alpha Thalassemia accounts for 60-90% of hydrops cases.[6]

Alpha Thalassemia is a group of syndromes that is characterized by deficient production of the α-globin chain due to deletions of the α-globin genes.[1-3] Each person normally has a total of four α-globin genes, two of which are encoded in tandem on each chromosome 16. Hemoglobin Bart's hydrops fetalis, characterized by a deletion of all four α-globin genes and expressed as (−−/−−), is the most severe and lethal form of thalassemia disease.[1,3] Generally, the inability to produce functional α-globin chains, which are critically required for fetal erythropoiesis to produce hemoglobin F (α2γ2), often leads to hydropic fetuses due to severe hypoxia making the condition incompatible with life.

In the Philippines, over 5% of the population are carriers of $\alpha^0$-thalassemia trait[1], characterized by two α-gene deletion, and most often from the same chromosome (heterozygous α-thalassemia 1). Majority of these cases, however, are being largely under diagnosed and under reported in our country due to the lack of effective screening, control, and management of the disease. This increases the risk of having partners that are both affected by the deletion of alpha globins and therefore increasing the risk of having a fetus affected by the spectrum of disease.

Data from the Thalassemia Center of the Philippines as of 2011 showed a total of 706 cases of Thalassemia in the country, with approximately 263 cases of Alpha Thalassemia carrier or trait, and 16 cases of hemoglobin H disease. This is the first reported case of a living hydrops fetalis secondary to hemoglobin Bart's in the country.

This case report intends to improve the clinicians' knowledge regarding the work up and management of pregnant patients diagnosed with hydrops fetalis, and increase the clinicians' awareness on the epidemiology, importance of targeted screening, and diagnosis of Alpha-Thalassemia in Filipino patients.

## CASE REPORT

Our patient is R.P.C, a 33-year-old, Filipino, Gravida 1 Para 0, at 29 4/7 weeks age of gestation, admitted due to palpitations. She has known history of anemia treated as

*1st place, 2016 Philippine Obstetrical and Gynecological Society (POGS) Interesting Case Paper Contest, August 18, 2016, 3rd Floor POGS Building, Quezon City

**Table 1**

| | 10 5/7 weeks | 23 2/7 weeks | 29 4/7 weeks | Reference Range |
|---|---|---|---|---|
| Hemoglobin | 95 | 118 | 88 | 120 - 160 g/L |
| Hematocrit | 0.30 | 0.36 | 0.28 | 0.36 - 0.47 |
| RBC | 4.39 | 5.53 | 4.04 | 4.20 - 5.40 x $10^{12}$/L |
| WBC | 7.8 | 8.10 | 16.7 | 4.5 – 10.0 x $10^{9}$/L |
| MCH | 22 | 21 | 22 | 27 – 32 pg |
| MCHC | 0.31 | 0.32 | 0.32 | 0.32 – 0.36 |
| MCV | 69 | 66 | 69 | 80 – 96 fL |
| RDW | 17.6 | 15.7 | 15.2 | 11.5 – 16.0 |
| Platelet | 300 | 242 | 237 | 140 – 440 |
| Neutrophil | 0.58 | 0.65 | 0.81 | 0.56 – 0.66 |
| Lymphocyte | 0.30 | 0.28 | 0.03 | 0.22 – 0.40 |
| Monocyte | 0.08 | 0.06 | 0.10 | 0.04 – 0.06 |
| Eosinophil | 0.04 | 0.01 | 0.06 | 0.01 – 0.04 |
| Basophil | 0.00 | 0.00 | 0.00 | 0.00 – 0.01 |

Iron Deficiency Anemia, however, she denies any history of abnormal bleeding or blood transfusion. Her family history, personal, and social history were unremarkable. At 10 5/7 weeks age of gestation, her complete blood count (CBC) showed normal hemoglobin and hematocrit levels for pregnancy, with microcytic and hypochromic RBCs (Table 1). Repeat CBC at 23 2/7 weeks age of gestation showed anemia with persistently low RBC indices. She was advised to continue taking her iron supplement and prenatal vitamins.

At 29 weeks age of gestation, her congenital anomaly scan revealed fetal cardiomegaly, mild pericardial effusion, and mild ascites (Figures 1 and 2). The rest of the findings were normal. She was then referred to a perinatologist and a pediatric cardiologist where a fetal 2D echo done (Figure 3) revealed normal cardiac structures, cardiomegaly, with the heart filling more than 80% of the thorax, trivial pericardial effusion, ejection fraction of 64% and slightly elevated aortic pressure signifying heart failure. Assessment at this time was fetal hydrops and fetal cardiomegaly. Close fetal monitoring and options for possible preterm delivery was put into place and she was given two doses of betamethasone 12 mg/IM to hasten fetal lung maturity in preparation for any eventuality.

At 29 4/7 weeks age of gestation, she developed easy fatigability, shortness of breath and palpitations. Her CBC revealed progression of her anemia (Table 1). She was subsequently admitted in the intensive maternal unit and blood transfusion was done for anemia correction. Thyroid function test, blood urea nitrogen, creatinine, urinalysis and total protein-albumin and globulin ratio ruled out any thyroid problem and Mirror Syndrome, which is a rare disorder affecting pregnant women with fetal hydrops. Her 2D-Echo and hemoglobin electrophoresis (Figure 4) revealed normal results.

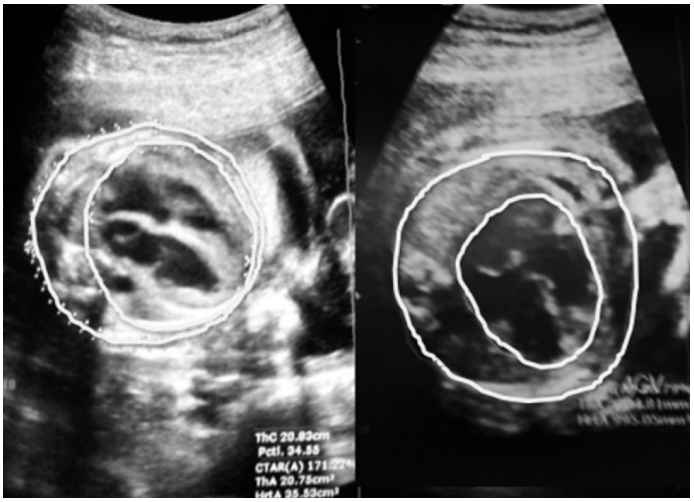

**Figure 1.** *RIGHT:* Congenital anomaly scan at 29 weeks age of gestation, showing cardiomegaly and mild pericardial effusion. The right and left outflow tracts can be visualized but the direction is not appreciated. There is no ventricular septal defect. Aortic arch not visualized. Superior and inferior vena cava drained into the right atrium (not shown). Mitral and tricuspid valve seen; *LEFT:* Ultrasound done 4 days later, at 29 4/7 weeks age of gestation, showing progression of the pericardial effusion and cardiomegaly with the heart now filling more than 80% of thorax

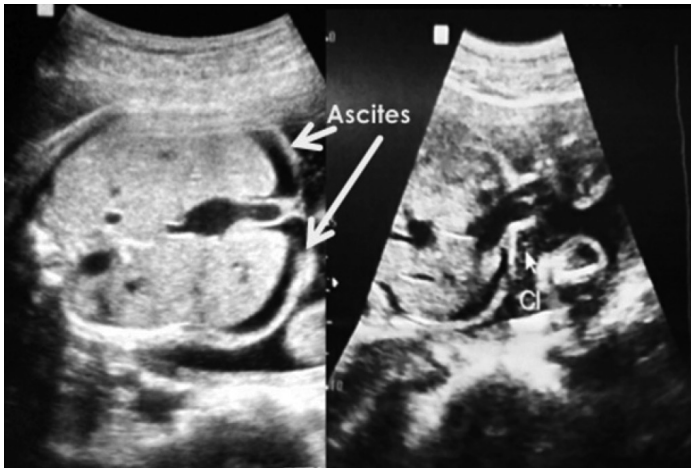


**Figure 2.** *RIGHT:* Congenital anomaly scan at 29 weeks age of gestation, showing mild ascites with intact diaphragm. There is a 3-vessel cord with intact cord insertion. Kidneys are normal in size and the bladder is fluid-filled; *LEFT:* Ultrasound done 4 days later, at 29 4/7 weeks age of gestation, showing progression of the fetal ascites as shown by the increased anechoic fluid in the fetal abdomen.

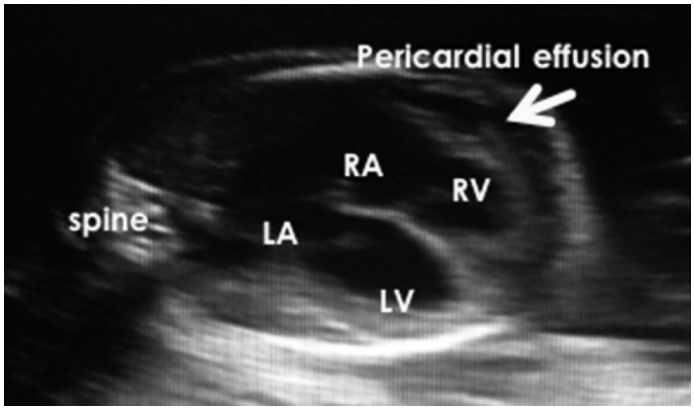


**Figure 3.** Fetal 2D echo done 29 weeks age of gestation, which revealed normal cardiac structures and ejection fraction, cardiomegaly with trivial pericardial effusion, and slight elevation of the aortic pressure signifying heart failure

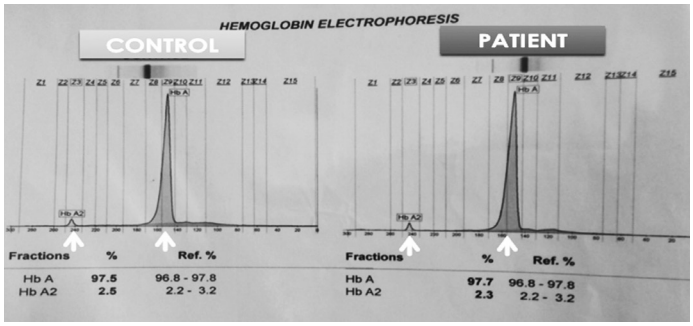


**Figure 4.** Maternal hemoglobin electrophoresis: The hemoglobin fractions A and A2 are within reference interval limits. No variants are detected. These findings are consistent with a normal hemoglobin electrophoresis pattern with a Mentzer Index of 16.98 cm

Work up for the possible etiology of fetal hydrops included an indirect Coomb's test, which revealed negative result. Doppler ultrasound showed normal fetal doppler indices, with peak systolic velocity of the middle cerebral artery (MCA) below the median for age of gestation, suggestive of absence of fetal anemia at the time of scan. Her TORCH panel, and RPR all revealed negative results. Parvovivurs-B19 determination was attempted, however it was not available.

Due to the observed progression of fetal ascites within three days, and persistent fetal cardiomegaly stemming from fetal heart failure, it was decided to deliver the baby in order to address the resuscitative efforts directly to the fetus. Magnesium sulfate 4 grams IV loading dose and 24-hour drip (1 gram/hr) was completed for neuroprotection and the patient delivered via low transverse cesarean section to a live, preterm, baby boy, APGAR score 4,7, birthweight 1090 grams, Maturity Testing 30 weeks, appropriate for gestational age (Figure 5).

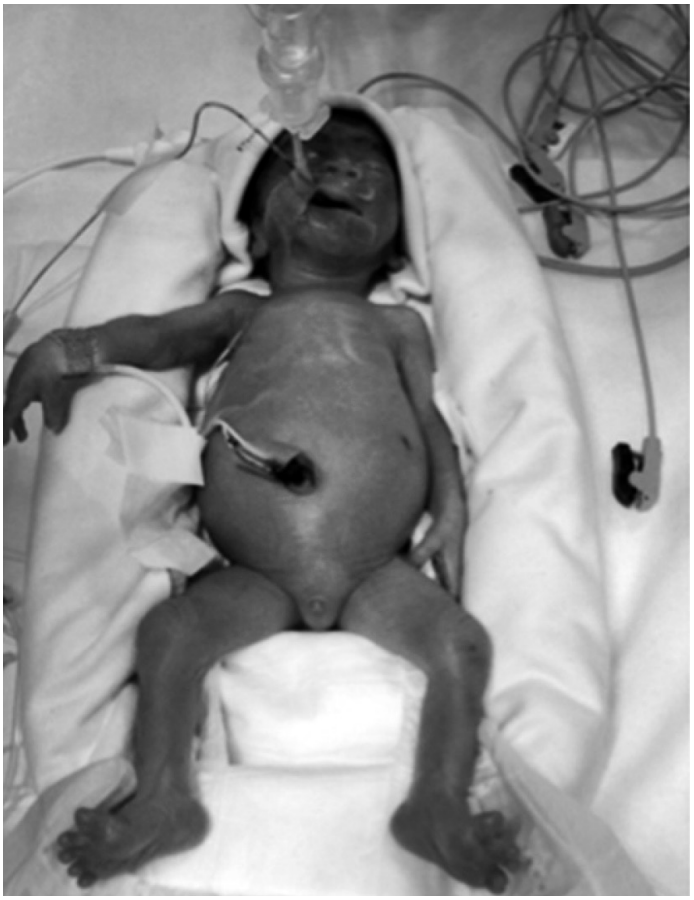

**Figure 5.** Fetal Hemoglobin Electrophoresis at 3 months old: Hemoglobin Bart's (42.6%), hemoglobin H (11.4%), and hemoglobin F (1.2%) accompanied by a decrease in the hemoglobin A and A2 fraction, indicative of Alpha Thalassemia phenotype. REMARKS: The presence of high levels of gamma tetramer and very low hemoglobin F in conjunction with high hemoglobin H and hemoglobin A2 are highly indicative of four α-chain deletion suggestive of hydrops fetalis.

At birth, the baby was noted to be anemic, mildly hydropic with globular abdomen distended with ascites, grossly male genitals and empty scrotal sac. There was no evidence of any organomegaly. He developed respiratory distress soon after birth and required intubation and surfactant therapy. He was started on inotropes to address the heart failure. Repeat 2D echocardiogram three hours post initiation of inotropes showed gross improvement in cardiac function, however, still poor with ejection fraction of 21%. There was multichamber dilation, severe tricuspid regurgitation, moderate mitral regurgitation, patent foramen ovale and ductus arteriosus (PDA), no pericardial effusion, and no pleural effusion. The baby responded well and after a turbulent neonatal ICU stay, medications and assisted ventilation were eventually weaned off on day 19 of life. There was reversal of the heart failure and fetal hydrops. Other complications of preterm delivery where addressed accordingly.

Further work up to determine the etiology of fetal hydrops was done including placental histopathology, which revealed placentomegaly (533 grams) and findings which ruled out any infection and placental anomaly. Blood typing ruled out Rh incompatibility (newborn "A+", mother "O+"), while Direct Coombs test revealed negative result. The baby's initial hemoglobin level was 87 mg/dl and the hematocrit was 0.39. He was transfused with washed and irradiated, Cytomegalovirus (CMV)-negative packed RBC for anemia correction. Peripheral blood smear showed hypochromia and marked anisocytosis. Expanded newborn screening revealed elevated levels for hemoglobinopathies and presence of hemoglobin Bart's indicative of a possible Hemoglobin H disease or Alpha Thalassemia. Hemoglobin electrophoresis (Figure 6) revealed presence of hemoglobin Bart's (42.6%), hemoglobin H (11.4%), and decreased hemoglobin F (1.2%), highly indicative of four α-globin chain deletion consistent with hemoglobin Bart's disease.

Both patients were referred to a hematologist and geneticist. A complete blood count was obtained from the husband, which revealed normal hemoglobin (149 mg/dl) and hematocrit (0.49), but with slightly microcytic and hypochromic RBCs (MCH 22 pg, MCHC 0.30, MCV 71 fL). Gene testing was done and both parents were confirmed to be positive for heterozygous $--^{SEA}$ $\alpha^0$-thalassemia mutation, indicative of a 2α-globin gene deletion on the same chromosome. Molecular testing of the offspring confirmed homozygous $--^{SEA}$ $\alpha^0$-thalassemia mutation on both chromosomes, indicative of a four α-globin gene deletion. The baby, however, was eventually discharged clinically well and stableon day 108 of life. The baby continues to survive past eight months of age, with no definite neurological deficits or developmental delay noted. Blood transfusion is being done to maintain hemoglobin level >100 mg/dL, with plans for possible stem cell or bone marrow transplant for definitive treatment, and to prevent complications of chronic blood transfusion.

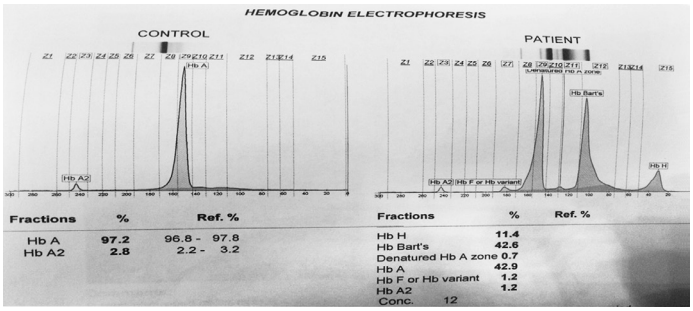


**Figure 6.** Fetal Hemoglobin Electrophoresis at 3 months old: Hemoglobin Bart's (42.6%), hemoglobin H (11.4%), and hemoglobin F (1.2%) accompanied by a decrease in the hemoglobin A and A2 fraction, indicative of Alpha Thalassemia phenotype. REMARKS: The presence of high levels of gamma tetramer and very low hemoglobin F in conjunction with high hemoglobin H and hemoglobin A2 are highly indicative of four α-chain deletion suggestive of hydrops fetalis.

## CASE DISCUSSION

Because of the wide use of anti-Rh prophylaxis, most cases (90%) of fetal hydrops are non-immune in origin.[5,6] Most common etiologies include cardiovascular (17-40%), chromosomal (15-20%), other structural fetal anomalies (15-20%), hematologic abnormalities (4-12%), followed by infection (5-7%), twin-twin transfusion syndrome (3-10%), metabolic and placental abnormalities (1%).[5,6,8] Fluid accumulation in the baby can result from obstructed lymphatic flow, cardiac failure, and/or extravasation of fluid either from increased intravascular hydrostatic pressure, decreased intravascular oncotic pressure or both.[5,8]

Fetal hydrops can be easily detected as early as the second trimester via ultrasonography, which reveals the presence of two or more abnormal fluid collections in the fetus. These include ascites, pleural effusions, pericardial effusion, and generalized skin edema defined as skin thickness >5 mm.[5,8] In this case, the patient presented with fetal ascites and pericardial effusion at 29 4/7 weeks. Increased placental thickness, defined as a placental thickness >4 cm in the second trimester or >6 cm in the third trimester[5] can be seen before the onset of hydrops at 12 weeks age of gestation.[3] Increased cardiac output, increased forward velocities in the ductus venosus, and increased peak systolic velocity of the MCA above 1.5 multiples of the median were documented in affected fetuses between 12-15 weeks' gestation.[3,5,8] These however were not evident in this case (Placental thickness 4.7 cm and normal Doppler studies).

Although many hydropic fetuses result to either

death in utero or mortality after delivery, it is a diagnostic challenge for obstetricians to work up and establish the etiology, rule out genetic disorders with a risk of recurrence in future pregnancies, and determine the appropriate management of affected pregnancies especially when it is viable and the condition is potentially reversible. Based on the guidelines by the Society for Fetal-Maternal Medicine, initial evaluation of the etiology of hydrops should include an antibody screen to rule out alloimmunization, and laboratory tests to rule out infection. Ultrasonography, which is used for the diagnosis, can be used together with fetal echocardiography to rule outcongenital, cardiac, and placental abnormalities, which are the most common causes of fetal hydrops.[5,6,8] The peak systolic velocity of MCA doppler has 90% sensitivity in evaluating for anemia from hematologic causes or even parvovirus.[5,8] Fetal karyotype or chromosomal microarray analysis by amniocentesis can also be done to rule out other possible causes of hydrops.[5,6,8]

In this case, a congenital scan that was done revealed structurally normal results, except for cardiomegaly and evidences of heart failure. It was decided to forego amniocentesis since it was more invasive and posed more harm to the patient and fetus.

Aside from the etiology, pregnancy management decisions depend on the gestational age that NIHF develops or was first identified. Antepartum surveillance in fetuses with NIHF can be done if the pregnancy has reached a viable gestational age, the underlying etiology of the hydrops is treatable, and the findings from surveillance will assist with delivery decisions.[5] For this patient, the plan was to address all preventable complications of preterm delivery before undergoing the planned early intervention in order to address the baby's failing heart, prevent progression of fetal hydrops and hopefully prevent fetal demise and possible maternal complications that may arise in her case. The decision to deliver was guided by the current fetal status, and the worsening of the sonographic findings of hydrops.

The prognosis of NIHF also depends on the underlying etiology, gestational age at detection and delivery, Apgar scores, and extent of resuscitation of the fetus.[5] Survival rate for pregnancies >20 weeks was approximately 50%, and only 25% survived without major morbidities.[5] In this case, the baby was diagnosed with fetal hydrops at 29 4/7 weeks age of gestation due tohemoglobin Bart's with $--^{SEA}$ deletion. This mutation deletes both α-globin genes but spares the embryonic gene, allowing enough functional embryonic hemoglobin to circulate and the phenotype of hydrops fetalis to develop[4]. After delivery, our patient responded well with resuscitative efforts and other complications of preterm delivery where addressed accordingly.

In Asia, α Thalassemia accounts for 60-90% of cases of hydrops fetalis and over 5% of the Philippine population are carriers of the disease.[7] Over 9 million carriers become pregnant annually and the risk that their partner is also a carrier ranges from 0.1-40% with a global average of 14%.[7] One of the most frequent α-thalassemia mutations includes the homozygous $--^{SEA}$ and $--^{FIL}$ mutation[4]. Despite the high prevalence of Thalassemia disease in Asia,[1,2,4,7] our health care system lacks an effective screening program targeted in the early identification, control, management and early counseling of patients who may be affected by the disease.

Our patient presented with history of anemia with microcytic and hypochromic RBCs (MCV <80). Early screening and work up for other causes of anemia could have allowed early detection of the couple's thalassemia trait status and allowed early planning and counseling for their future pregnancies. Berghella et al. provided an algorithm to screen patients who may be at risk of being affected by the disease (Figure 7). A simple complete blood count including the RBC indices can be used to screen patients for the presence of anemia and low mean cell volume (MCV<80 fL). Ferritin levels can be requested to differentiate iron deficiency anemia

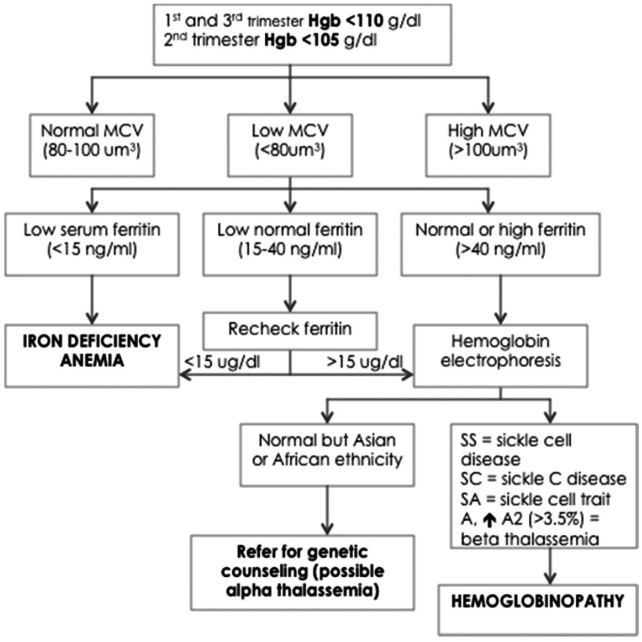


**Figure 7.** Source: Berghella, V. (2012). Maternal-Fetal Evidence Based Guidelines (Vol. 2nd Edition). London, UK: Informa Healthcare.
Algorithm for workup and screening of anemia in pregnancy. For normal MCV, check reticulocyte count to determine if anemia is secondary to underproduction, chronic diseases, or hemolysis. For high MCV, work up patient for possible etiology of macrocytic anemia (ie. Folate or Vitamin B12 deficiency).

(IDA) from hemoglobinopathies, with the latter showing normal or high ferritin levels (>40 ng/mL).[8] Hemoglobin electrophoresis is then done to rule out Beta-Thalassemia or Sickle cell disease. Once IDA has been excluded, and hemoglobin electrophoresis is normal, genetic testing isdone to detect α-globin gene deletions that are characteristic of α-Thalassemia especially in African and Asian ancestry.[8] Genetic screening is an important aspect of prenatal care in this condition since parents who are carriers of the $a^0$-thalassemia trait have a 25% risk of having an offspring affected with Hemoglobin Bart's disease.

Although the prognosis of hydrops fetalis surviving to term or even after birth is guarded, reported cases of those who survived have favorable outcome depending on the cause. Five reported cases of survivors of hemoglobin Bart's hydrops fetalis[9] are currently on an intensive transfusion strategy to increase functional hemoglobin, reduce tissue hypoxia, and hemolysis overtime. However, due to the advances in medicine, there were also reported cases of survivors who underwent successful cord blood[10] and bone marrow transplantation[11], with favorable prognosis and currently does not require blood transfusion to maintain hemoglobin levels >100 mg/dL, which paves another therapeutic option for our patient.

## SUMMARY

The cornerstone of counseling and management of fetal hydrops is a thorough evaluation of its underlying etiology. Work up for treatable causes and the gestational age upon diagnosis greatly affects the management decisions of affected pregnancies. Also, given the prevalence rate of thalassemia in our country, this warrants an effective implementation of targeted public awareness program, antenatal screening program and prenatal diagnostic service since Filipinos have a high risk of being affected by the disease. An international clinical registry of surviving fetal hydrops with comprehensive evaluation and management of all related aspects could provide evidence-based guidance for managing this condition in future cases. ■

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