Cases Report

Noninvasive Diagnosis of Fetal Anemia and Fetal Intravascular Transfusion Therapy: Experiences at Siriraj Hospital

Tuangsit Wataganara MD*, Booraya Wiwanichayakul MD*,
Pornpimol Ruengwuttilert MD, PhD*, Prasert Sunsaneevithayakul MD*,
Sommai Viboonchart BN*, Charnchai Wantanasiri MD*

** Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University*

Traditionally, when fetal hydrops are found along with certain markers indicating fetal anemia, fetal blood sampling would be performed through cordocentesis to confirm the diagnosis. This procedure, however, comes with an inherent risk of losing the whole pregnancy. When anemia was verified, treatment options were limited and the prognosis was grim. In this article, the authors described their experiences of using prenatal Doppler studies as a noninvasive venue in the diagnosis and treatment of fetal anemia. Once the diagnosis of fetal anemia is made, the patient will be asked to undergo an algorithm to investigate the definite cause of anemia, along with simultaneous ultrasound-guided intravascular fetal transfusion in selected cases. The authors selected two cases of fetal anemia of different etiologies and treatment outcomes to demonstrate the significance of early diagnosis and intervention. Review of the relevant medical literatures and the proposed algorithms were also provided.

Keywords: *Hydrop fetalis, Fetal anemia, Fetal therapy, Isoimmunization, In utero transfusion*

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Hydrops fetalis poses a unique dilemma for all practicing obstetricians. This generalized fluid collection within the fetal body can be categorized into immune-related and unrelated causes. Immune hydrops originates from isoimmunization from blood group incompatibility between the fetus and the mother and this leads to substantial destruction of fetal red blood cells. In a severely anemic fetus, the heart fails to accommodate and edematous changes follow.

Ultrasound markers can be suggestive of the anemic cause of hydrops. Fetal hepatosplenomagaly, along with placentomegaly could be found as a result of compensating extramedullary hemopoiesis in these organs. Cardiomegaly could presage the development of fetal congestive heart failure. However, none of these findings are specific to an anemic fetus. Magi et al reported in their multi-center study that an increased peak systolic velocity in the middle cerebral artery is related to a decreased blood viscosity found in anemic fetuses[1]. The results have been reproducible, and Doppler studies of fetal vessels have proven to be a powerful tool in the management of fetal anemia[2].

The authors have developed a novel algorithm in our Maternal-Fetal Medicine unit to provide a systemic and uniform clinical care for the hydropic fetuses caused by severe anemia, as shown in Fig. 1. In summary, any fetus with ultrasound findings suggestive of fetal anemia will receive Doppler studies of the middle cerebral artery. If Doppler studies suggested fetal anemia, fetal blood sampling simultaneously with red blood cell transfusion was performed. In the present article, the authors described these innovative procedures and presented 2 cases of fetal anemia diagnosed

Correspondence to : Wataganara T, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. Phone: 0-2419-7000, Fax: 0-2418-2662, E-mail: sitwg@mahidol.ac.th

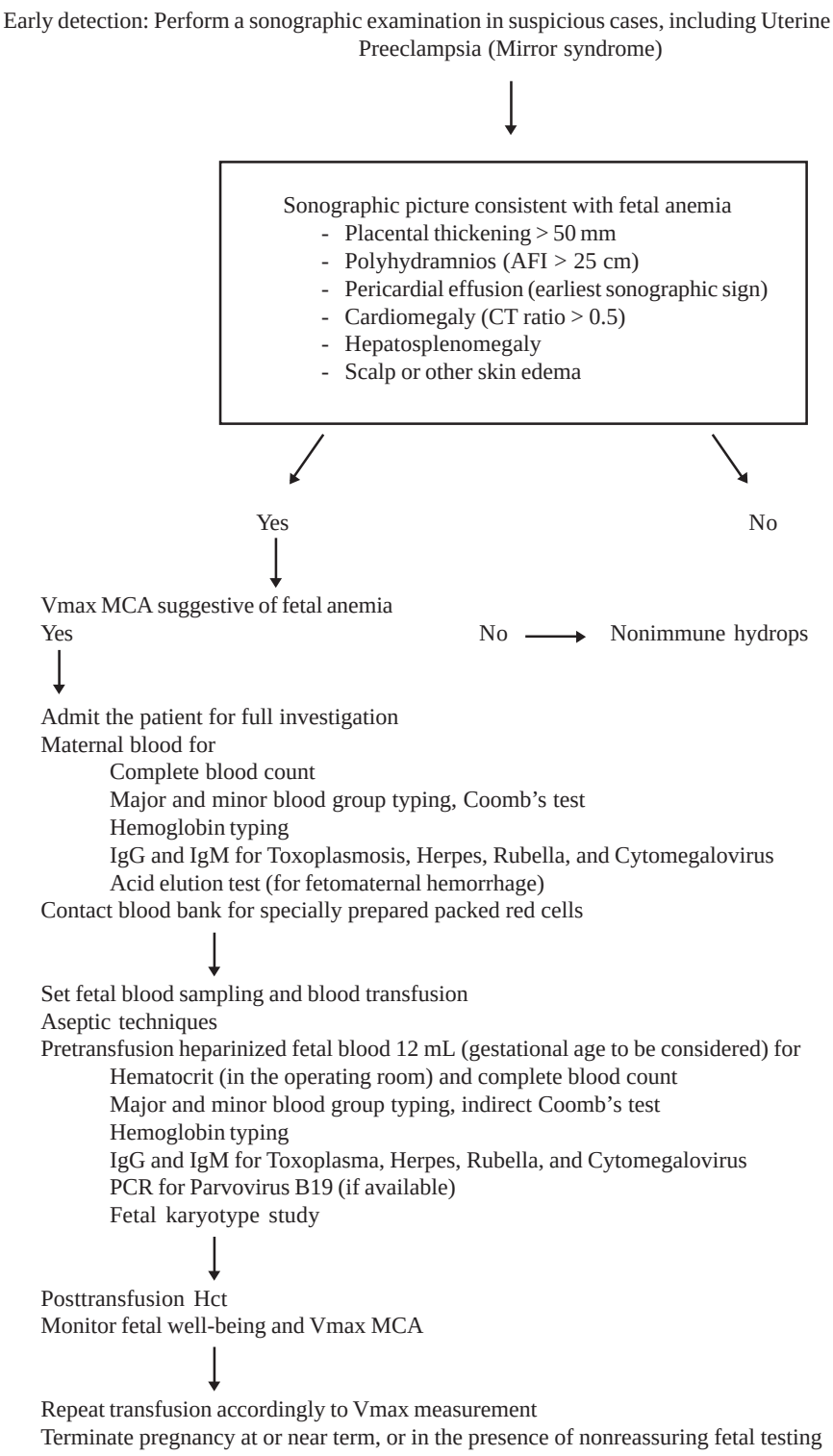

Fig. 1 Algorithm for the management of red blood cell isoimmunization during pregnancy using Vmax MCA and in utero transfusion

by Doppler studies and received *in utero* transfusion in the authors' unit. Global experiences along with future prospects are also discussed.

Measurement of maximum velocity flow (Vmax) of fetal middle cerebral artery

The techniques for measuring the Vmax MCA have been described previously[3], but may be summarized as follows. The authors used Toshiba Aplio (Tokyo, Japan) for the Doppler studies. Power Doppler was applied for a better delineation of the vessel. The whole diameter of the vessel was included in the Doppler gate. Ultrasound probe was manipulated in a way to ensure the 0 angle between the ultrasound beam and the direction of blood flow. If this angle could not be achieved, an angle adjustment was accomplished using an angle correction function in Doppler mode. Vmax of above 1.5 multiple of the median (MoM) at particular gestational age is highly suggestive of fetal anemia, and hence fetal blood sampling was performed simultaneously with fetal red blood cell transfusion[1]. An example of Vmax measurement is shown in Fig. 2.

Investigations of fetal blood to define the cause of anemia

The authors used 20-G spinal needle for fetal blood sampling and transfusion in our unit. Cord insertion is preferred to the free loop, especially if the transfusion is to be followed. Aseptic technique is mandatory for the ultrasound-guided puncture of umbilical vein. Once the needle is in place, fetal blood was drawn for complete investigation as described in Fig. 1.

Fetal red blood cell transfusion

The authors used packed red blood cells with hematocrit of 80% for fetal transfusion. The blood bank prepared this unit from group O blood, screening negative for blood borne infection diseases including syphilis, hepatitis B, HIV, cytomegalovirus, and toxoplasmosis. Required transfusion volume (A) was calculated by the following formula

$$Ht = [(Hi)(V) + (Hp)(A)] / (V + A)$$

Where: Ht = posttransfusion hematocrit
Hi = initial fetal hematocrit
V = pretransfusion fetal-placental blood volume
Hp = Hematocrit of donor packed cells
A = volume of donor packed cells transfused or withdrawn
V + A = blood volume of fetoplacental unit after each addition or withdrawal of blood

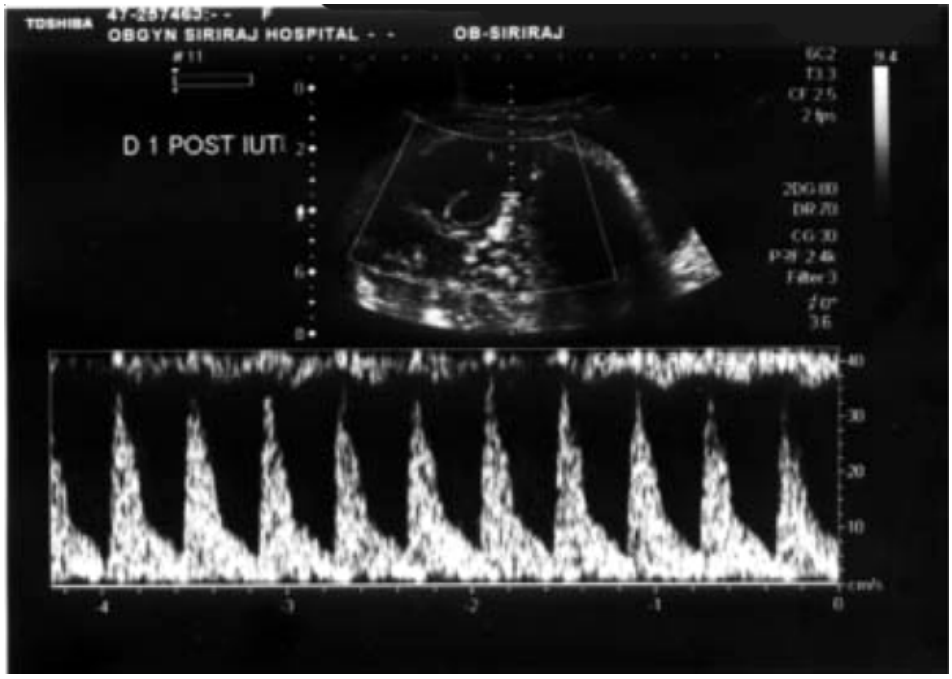

Fig. 2 Vmax MCA measurement: Description

The authors calculated the fetoplacental blood volume using Morris's estimation of 160 mL per kilogram of estimated fetal weight. The real fetal hematocrit was obtained at the time of blood sampling, and the calculation for the transfusion volume was made immediately, based on the desired posttransfusion hematocrit of 60-70%. Blood could be directly transfused into the umbilical vein. However, if the required transfusion volume was sizable, the authors would perform an *in utero* exchange transfusion. Fig. 3 shows the ultrasound picture during the transfusion.

Cases Report

Case 1

This is a 29-year-old pregnant woman, in her third pregnancy, with a history of losing her second baby *in utero* from an undetermined cause, and was delivered by Cesarean section due to failed induction of labor at term. In the current pregnancy, she had her antenatal care at the institute until the gestational age of 32 3/7 weeks' when the fetus was diagnosed with hydrops fetalis. Generalized skin edema, along with massive pleural effusion, ascites and placentomegaly were found. The umbilical vein was dilated, as shown in Fig. 4. Vmax MCA was 100 cm/s, which is well above the 1.5 MoM range of Vmax at 32 weeks'. The authors were able to transfuse only 40 mL of packed red blood cells before the needle displaced, and fetal hematocrit was raised from 19% to 35%. Laboratory results from maternal and fetal blood samples are shown in Table 1.

Improvement of Vmax MCA was noticed immediately following the transfusion. The patient was observed in-house overnight, and found to have uterine contractions which did not respond to tocolytic treatment. Vmax MCA the following day was 30 cm/s, as shown in Fig. 2. She underwent a Cesarean section the following day, giving birth to a baby boy who weighed 2,390 grams, with an Apgar score of 2 and 5 at 1 and 5 minute, respectively. The baby was admitted to the neonatal intensive care unit for 11 days, and recovered with a mild degree of bronchopulmonary dysplasia. The baby was hemoglobin Constant Spring homozygote, which has never been reported to cause severe anemia. He received another exchange transfusion immediately after birth to support his vital signs and has not suffered from anemia again since.

Case 2

This is a 19-year-old lady, in her primigravidarum, presented at our institute at the gestational age of 30 2/7 weeks' after her primary physician gave the diagnosis of fetal hydrops. Detailed sonogram in the study unit revealed generalized skin edema with mild pleural effusion. Cardiomegaly, hepatosplenomegaly, and placentomegaly were also noticed. Vmax MCA was 81 cm/s, which is well above 1.5 MoM that of 30 menstrual weeks'. The mother's 2,6-dichlorophenolindophenol precipitation (DCIP) test was negative. While the hemoglobin typing of both parents was pending, the authors decided to perform fetal blood sampling, followed by transfusion with 70 mL packed red cells to salvage the fetus. Vmax MCA was brought down to 40 cm/s following the procedure, and the patient was allowed to go home the next day, with a schedule to weekly monitor Vmax MCA. However, the fetal hemoglobin typing came back to be invariably lethal hemoglobin Bart's. Spontaneuos minimal fetomaternal hemorrhage was also found from acid elution test. After thorough counseling, the couple opted for termination of the pregnancy. Fetal autopsy was not available.

Discussion

The advance of sonographic technology and the better understanding of fetal physiology have remarkably improved the efficacy of prenatal diagnosis. The diagnosis of fetal anemia, leading to heart failure, could reliably be made by Doppler study of fetal vessels, as demonstrated in the authors' 2 presented cases. This diagnostic venue allows us to noninvasively identify the anemic cause of fetal hydrops, and hence, eliminate the 2-percent inherent risk of fetal loss from diagnostic cordocentesis[4]. In addition, once anemia is identified from the Doppler studies, blood transfusion to salvage the fetus could be performed simultaneously with the fetal blood analysis. The techniques are described in the present article.

Fetal anemia could be a consequence of a variety of diseases. The dilution of blood results in faster flow, and could be demonstrated by an increased circulation velocity. In theory, Doppler studies could be performed at any desired fetal vessels, however most studies have been focused on two major vessels: the middle cerebral artery and the intrahepatic portion of umbilical vein. The technical convenience and the reproducibility to obtain an adequate Doppler shift results are the main reasons these vessels are heavily studied[2]. In the unit, the authors used the nomogram developed by Magi et al, that is the Vmax of more than 1.5 multiple of the medians at a particular gestational age is highly suggestive of fetal anemia[1]. Using this technique, we were able to diagnose fetal anemia accurately in both cases. Some investigators have defined

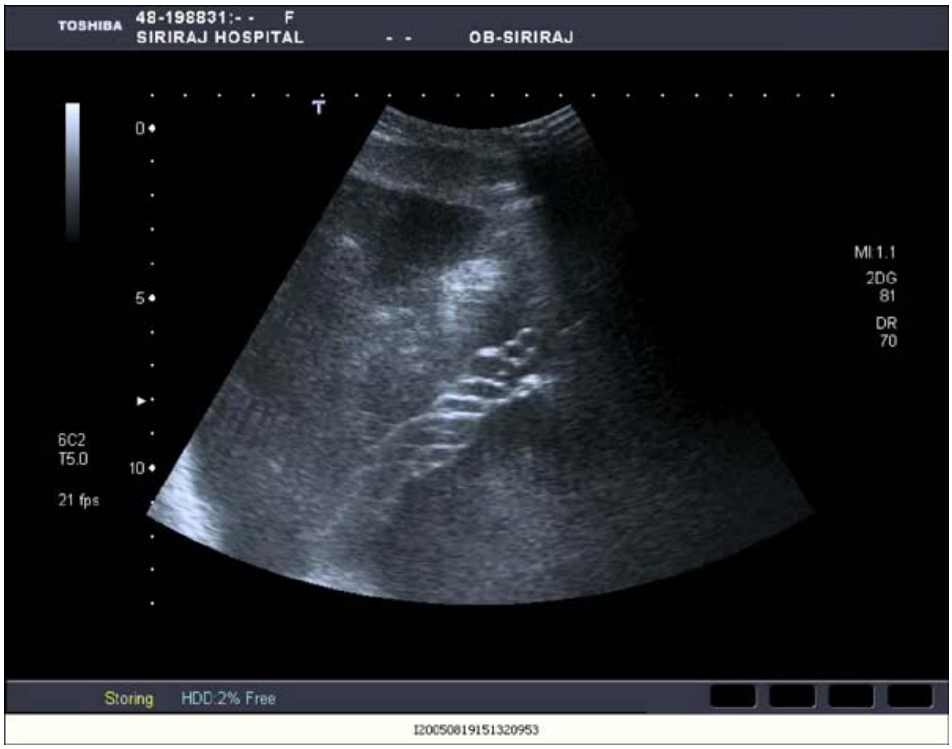

Fig. 3 Ultrasound picture during the transfusion

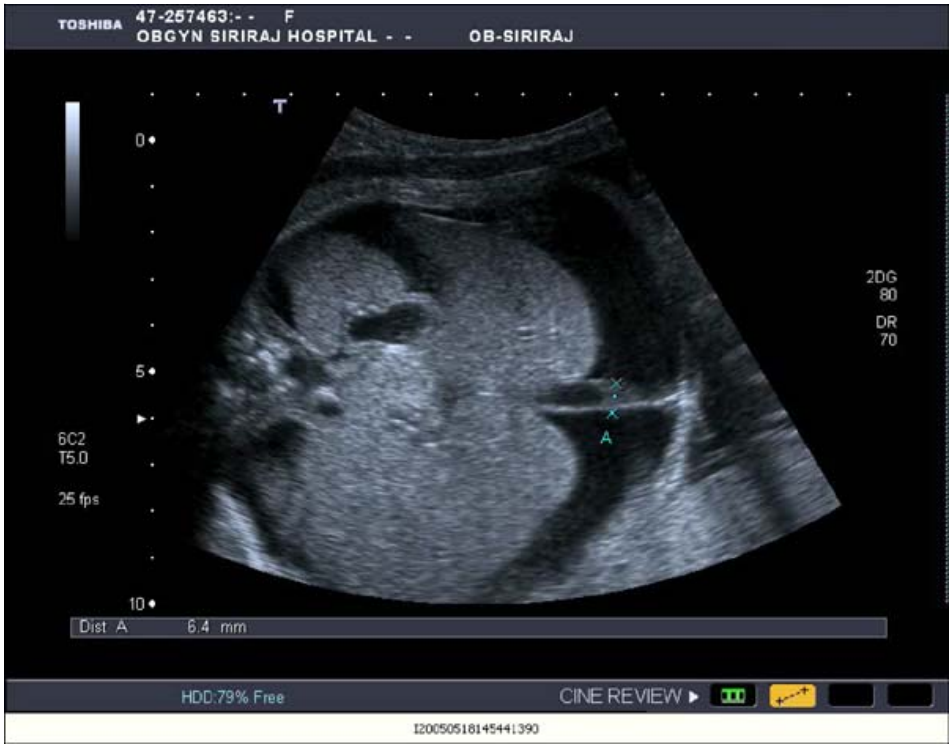

Fig. 4 Massive fetal ascites with dilated umbilical vein

Table 1. Summary of the 2 presenting cases

	Patient 1	Patient 2
Maternal age (yrs)	29	19
Gestational age upon the diagnosis	32 3/7	30 2/7
Vmax MCA (cm/s)		
Before IUT	100	81
After IUT	30	40
Maternal blood test	Blood group O, Rh+	Blood group B, Rh+
	Direct Coomb's test weakly positive	Direct Coomb's test Negative
	Hemoglobin CS trait	α-thalassemia 1 trait
	Rubella IgM Negative	Rubella IgM Negative
	Rubella IgG Negative	Rubella IgG Negative
	HSV IgM Negative	HSV IgM Negative
	HSV IgG Positive	HSV IgG Positive
	CMV IgM Negative	CMV IgM Negative
	CMV IgG Positive	CMV IgG Positive
	Toxoplasma IgM Negative	Toxoplasma IgM Negative
	Toxoplasma IgG Negative	Toxoplasma IgG Negative
	Acid elution test Negative	Acid elution test Fetal hemorrhage 15 mL
Fetal blood test		
Hct Pretransfusion	19%	20%
Posttransfusion	35%	67%
	Blood group A, Rh+	Blood group B, Rh+
	Hemoglobin CS trait	Hemoglobin Bart's 95%
	Rubella IgM Negative	Rubella IgM Negative
	Rubella IgG Negative	Rubella IgG Negative
	HSV IgM Negative	HSV IgM Negative
	HSV IgG Positive	HSV IgG Positive
	CMV IgM Negative	CMV IgM Negative
	CMV IgG Positive	CMV IgG Positive
	Toxoplasma IgM Negative	Toxoplasma IgM Negative
	Toxoplasma IgG Negative	Toxoplasma IgG Negative
	Fetal karyotype: 46, XY	Fetal karyotype: 46, XY
Transfusion volume (mL)	70	80
Diagnosis	Hb CS homozygote	Hb Bart's disease
Pregnancy outcome	C-section at 35 weeks'	Termination of pregnancy
	11-day NICU	
	Discharged uneventfully	

an increased Vmax to be above 90 percentiles at each gestational age[5].

Traditionally, the severely anemic fetuses were delivered prematurely, followed by postnatal blood transfusion. These babies would face unavoidable complications due to premature birth, and many of those, if they survived, would be suffering from long term neurological deficits and other complications of prematurity. Due to technological advancement, the development of fetal hydrops from the anemic state is now considered salvageable. In utero red blood cell transfusion could prevent fetal death and defer the

termination to near term as much as possible. If anemia persists, transfusion prior to delivery could improve the odds of neonatal resuscitation and the requirement of NICU care[2]. Thus, in utero transfusion could improve neonatal survival overall. One major exception of this, especially in Thailand, is the invariably lethal hemoglobin Bart's hydrops fetalis. Therefore, hemoglobin typing of both parents and the fetus is vital for the management, even in the light that the screening test is negative, as in Case 2.

In Case 1, the cause of fetal anemia was not identified after thorough investigations. The authors are reluctant to believe that the finding of homozygous hemoglobin constant spring (Hb CS) is the sole cause of hydrops since it has never been reported to cause severe anemia, and this baby did not suffer from anemia at the age of 3 months. It is possible that the interaction between this homozygous Hb CS and certain unidentified factors in utero might explain severe fetal anemia in this case.

Measurement of Vmax MCA allows the authors to detect fetal anemia frequently as needed, without compromising the fetal condition. The authors' proposed algorithm for the management of isoimmunized pregnant women is shown in Fig. 1. The authors are using the MCA and not the intrahepatic umbilical vein, as the target for Doppler studies due to the technical convenience and its predictable response following the transfusion[6]. In cases at risk, for instance, when the mother is isoimmunized, the following of Vmax MCA could suggest fetal anemia, and thus, fetal transfusion could be performed even before the onset of fetal heart failure and hydrops. Immediate improvement of Vmax MCA in our two presenting cases supports its use as a noninvasive venue to monitor fetal hematocrit[7].

In conclusion, the authors' preliminary report has shown a prospect of using an integrated algorithm of Doppler studies and in utero transfusion in the management of fetal anemia. Even though the measurement of maximal velocity flow is noninvasive, the ability to obtain an accurate result and an appropriate interpretation require rigorous training. Extensive counseling to the worrying parents is crucial in this fetal diagnosis and therapy scheme. Complications from the procedure, such as cord hematoma or fetal exsanguinations, must be properly handled. Better understanding of fetal physiology and accumulating experiences could finally translate into sound care for the unborn patient.

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แนวทางการวินิจฉัยภาวะโลหิตจางของทารกในครรภ์และการรักษาโดยการถ่ายเลือด; ประสบการณ์ในโรงพยาบาลศิริราช

ตวงสิทธิ์ วัฒกนารา, บูรยา ไววานิชยกุล, พรพิมล เรืองวุฒิเลิศ, ประเสริฐ ศันสนียวิทยกุล, สมหมาย วิบูลชาติ, ชาญชัย วันทนาศิริ

ในอดีตนั้น การวินิจฉัยภาวะโลหิตจางของทารกในครรภ์สามารถทำได้โดยการเจาะตรวจเลือดสายสะดือหลังจากตรวจพบว่าทารกนั้นบวมน้ำ และมีการตรวจพบทางคลื่นเสียงความถี่สูงบางประการที่ชี้บ่ง การเจาะตรวจเลือดสายสะดือนั้นถือเป็นหัตถการที่มีความเสี่ยงต่อการเสียชีวิตของทารก พยากรณ์โรคของทารกที่มีภาวะโลหิตจางจนบวมน้ำมักไม่ดีนัก เนื่องจากไม่มีวิธีการรักษาที่ได้ผลดี ในบทความนี้ คณะผู้นิพนธ์ได้นำเสนอแนวทางการตรวจวินิจฉัยภาวะทารกโลหิตจางในครรภ์โดยอาศัยการตรวจด้วยคลื่นเสียงความถี่สูงดอปเปลอร์ หลังจากทารกได้รับการวินิจฉัยว่ามีภาวะซีดจากการตรวจด้วยคลื่นเสียงความถี่สูงดอปเปลอร์ ทารกจะได้รับการเจาะเลือดสายสะดือเพื่อยืนยันการวินิจฉัยและสาเหตุ พร้อมไปกับการเปลี่ยนถ่ายเลือดของทารกในครรภ์ คณะผู้นิพนธ์ยังได้บรรยายถึงการใช้คลื่นเสียงความถี่สูงดอปเปลอร์ในการตรวจติดตามภาวะโลหิตจางของทารกภายหลังการเปลี่ยนถ่ายเลือดเป็นระยะ ๆ โดยที่ไม่ต้องเจาะเลือดสายสะดือทารกซ้ำ อันเป็นการลดความเสี่ยงต่อการสูญเสียการตั้งครรภ์ นอกจากนั้นยังได้มีการยกตัวอย่างทารกสองรายที่มีภาวะโลหิตจางจากสาเหตุต่างกันเพื่อประกอบความเข้าใจ รวมถึงได้มีการทบทวนหลักฐานทางการแพทย์ที่เกี่ยวเนื่องอันชี้บ่งถึงความเป็นไปได้ในการใช้แนวทางการดูแลดังกล่าวกับทารกที่สงสัยว่ามีภาวะโลหิตจางต่อไปในอนาคต