CASE REPORT

UDC: 618.39-021.3-074
DOI: 10.2298/VSP150605130D

Massive fetomaternal hemorrhage as a cause of severe fetal anemia

Opsežna fetomaternalna hemoragija kao uzrok teške anemije fetusa

Aleksandar Dobrosavljević*, Jelena Martić[†‡], Snežana Rakić*[‡], Vladimir Pažin*[‡], Svetlana Janković Ražnatović*[‡], Svetlana Srećković[§], Branko Dobrosavljević[‖]

***Clinic of Obstetrics and Gynecology "Narodni front", Belgrade, Serbia; [†]The Institute for Medical Care of Mother and Child of Serbia "Dr Vukan Čupić", Belgrade, Serbia; [‡]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [§]Clinic for Orthopedic Surgery, Clinical Center of Serbia, Belgrade, Serbia; [‖]Private Gynecological Practice "Demetra", Loznica, Serbia**

Abstract

Introduction. Fetomaternal hemorrhage (FMH) is a transfusion of fetal blood into the maternal circulation. A volume of transfused fetal blood required to cause severe, life-threatening fetal anemia, is not clearly defined. Some authors suggest volumes of 80 mL and 150 mL as a threshold which defines massive FMH. Therefore, a rate of massive FMH is 1 : 1,000 and 1 : 5,000 births, respectively. Fetal and neonatal anemia is one of the most serious complications of the FMH. Clinical manifestations of FMH are nonspecific, and mostly it presented as reduced fetal movements and changes in cardiotocography (CTG). The standard for diagnosing FMH is Kleihaurer-Betke test. **Case report.** A 34-year-old gravida (G) 1, para (P) 1 was hospitalized due to uterine contractions at 39 weeks of gestation. CTG monitoring revealed sinusoidal fetal heart rate and clinical examination showed complete cervical dilatation. Immediately after admission, the women delivered vaginally. Apgar scores were 1 and 2 at the first and fifth minute, respectively. Immediately baby was intubated and mechanical ventilation started. Initial analysis revealed pronounced acidosis and severe anemia. The patient received intravenous fluid therapy with sodium-bicarbonate as well as red cell transfusion. With all measures, the condition of the baby improved with normalization of hemoglobin level and blood pH. Kleihaurer-Betke test revealed the presence of fetal red cells in maternal circulation, equivalent to 531 mL blood loss. The level of maternal fetal hemoglobin (HbF) and elevated alpha fetoprotein also confirmed the diagnosis of massive FMH. **Conclusion.** For the successful diagnosis and management of FMH direct communication between the obstetrician and the pediatrician is necessary as presented in this report.

Key words:
fetomaternal transfusion; anemia; fetus; newborn; apgar score; diagnosis; intensive care, neonatal; treatment outcome.

Apstrakt

Uvod. Fetomaternalna hemoragija (FMH) se definiše kao prelazak krvi ploda u cirkulaciju majke. Volumen fetalne krvi koji je neophodan da pređe u cirkulaciju majke i izazove tešku fetalnu anemiju nije precizno definisan. Većina autora sugeriše masivnu fetomaternalnu transfuziju pri volumenu od 80 mL odnosno 150 mL fetalne krvi, te je stopa FMH 1 : 1 000, odnosno 1 : 5 000 porođaja. Fetalna i neonatalna anemija je jedna od najozbiljnijih komplikacija FMH. Kliničke karakteristike FMH su nespecifične i najčešće se manifestuju redukcijom fetalnih pokreta i promenama u kardiotokografskom (CTG) zapisu. Dijagnostički standard FMH je Kleihaurer-Betke test. **Prikaz bolesnika.** Trudnica, stara 34 godine, primljena je na kliniku radi porođaja. CTG zapis bio je sinusoidalnog tipa dok je akušerskim pregledom konstatovana kompletna cervikalna dilatacija. Neposredno nakon prijema trudnica se vaginalno porodila. Apgar skor u prvom i petom minutu iznosio je 1 i 2. Odmah je sprovedena reanimacija, intubacija i mehanička ventilacija. Inicijalne gasne analize ukazivale su na to da se radi o teškoj acidozi i anemiji. Uz sve primenjene mere stanje novorođenčeta se stabilizovalo, uz normalizaciju vrednosti hemoglobina i pH vrednosti krvi. Kleihaurer-Betke testom ustanovljena je FMH u vrednosti od 531 mL. Povišene vrednosti fetalnog hemoglobina (HbF) kao i alfa fetoproteina u majčinoj krvi potvrdile su da se radilo o FMH. **Zaključak.** Za uspešnu dijagnozu i lečenje FMH neophodna je i direktna komunikacija između akušera i pedijatra kao što je prokazano u ovom slučaju.

Ključne reči:
transfuzija, fetomaternalna; anemija; fetus; novorođenče; apgar skala; dijagnoza; intenzivna nega, neonatalna; lečenje, ishod.

Correspondence to: Aleksandar Dobrosavljević, Clinic of Obstetrics and Gynecology "Narodni front", Kraljice Natalije 62, 11 000 Belgrade, Serbia. E-mail: dobrosavljevical@gmail.com

Introduction

Fetomaternal hemorrhage (FMH) is a transfusion of fetal blood into the maternal circulation. It is well-known that placenta enables communication between mother and fetus in both directions, but in almost all pregnancies a small amount of fetal blood enters into the maternal circulation. Normal volume of fetal blood detected in maternal circulation is under the 0.1 mL [1]. A volume of fetal blood that requires to be transfused into the maternal circulation and that causes severe, life-threatening anemia in a fetus, i.e. newborn, is not clearly defined. Therefore, various criteria are used to define massive FMH. Many authors suggest volumes of 80 mL and 150 mL as a threshold to define massive FMH, which is estimated to occur in 1 in 1,000 and 1 in 5,000 deliveries, respectively [2]. Etiology is idiopathic, but some conditions may predispose to FMH like some obstetrical procedures, and placental abruption. Clinical presentation of FMH during pregnancy is nonspecific, mostly presented as reduced fetal movements and changes in cardiotocography (CTG) [3]. Diagnosis of FMH may be established by the Kleihauer-Betke test, the standard method for detection and quantification of fetal blood in the maternal circulation. A prompt and appropriate treatment increases the survival rate, while a long-term prognosis is uncertain.

In this report, we presented a case of massive FMH in term pregnancy, resulted in severe neonatal anemia and asphyxia and confirmed by Kleihauer-Betke (KB) test.

Case report

A 34-years-old gravida (G) 1, para (P) 1 was hospitalized due to uterine contractions at 39 weeks of gestation. Pregnancy was uneventful until two days before delivery, when the patient noticed diminished fetal movements, general weakness with mild fever and discrete joint pains. The patient was admitted to the hospital isolation unit with the diagnosis of viral upper respiratory tract infection. The patient did not suffer from any chronic illness, and never had surgical procedures. CTG monitoring revealed sinusoidal fetal heart rate (Figure 1) and clinical examination showed intact membranes and complete cervical dilatation with the head in occipital anterior presentation with a small fontanel at +1 cm in relation to the interspinal line. After amniotomy, amniotic fluid was clear and immediately after admission the women delivered vaginally a female newborn weighted 2,900 g. Apgar scores were 1 and 2 at the first and fifth minute, respectively. The infant was very pale, flaccid, without respiratory effort, bradycardic heart rate 40 beats *per* minute (bpm). Resuscitation started immediately, the baby was intubated and mechanical ventilation started. Initial blood gas analysis revealed pronounced acidosis with pH 6.8, pO_2 5.3 kPa, pCO_2 7.7 kPa, lactate level of 19.4 mmol/L and non-measureable base deficit. Complete blood count analysis showed severe anemia with the hemoglobin level of 5.7 g/dL, red blood cell number $1.47 \times 10^6/mm^3$, hematocrit 16% and marked reticulocytosis of 17.4%. The infant and the mother had the same blood O group, Rh- negative, and negative Coombs test. There were no signs of hydrops and hyperbilirubinemia. Intravenous fluid therapy with sodium-bicarbonate started as well as empirical antibiotic therapy (ampicillin and amikacin). On the first hospital day, the patient received two packed red cell transfusion. The infant received the third packed red cell transfusion on the second day of hospitalization. Sepsis screen was normal, as well as ultrasonography of the brain and the abdomen. With all these measures, the condition of the baby improved with normalization of the level of hemoglobin and blood pH. Mechanical ventilation was stopped on the third day of hospitalization. Electroencefalography showed normal activity, without specific changes. The infant was discharge from hospital on the 9th day in good general condition. Considering that hemolytic disease of the newborn and other most common causes of neonatal anemia were excluded, Kleihaurer-Betke test was performed due to suspicion of FMH. This analysis revealed the presence of fetal red cells in maternal circulation, equivalent to 531 mL blood loss. The level of maternal fetal hemoglobin (HbF) was 4.85% (normal less than 2%), and elevated alpha fetoprotein 4,214 IJ/ml also confirmed the diagnosis of massive FMH.

Discussion

Fetomaternal hemorrhage is still a poorly understood condition which can result in severe fetal anemia leading to life-threatening newborn illness with high mortality and significant morbidity [4]. There are different standpoints regar-

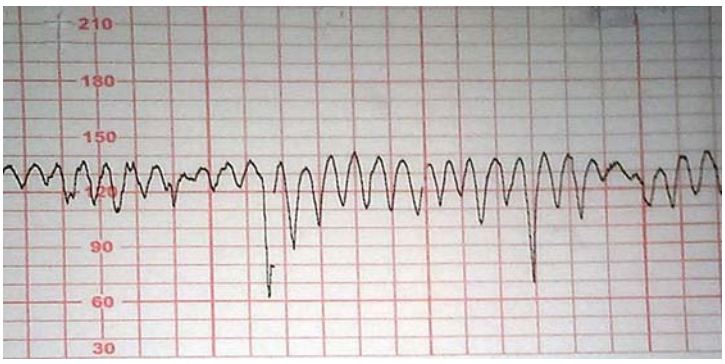

Fig. 1 – Sinusoidal cardiotocography (CTG) of the patient with oscillation amplitude which is slightly higher than a typical one (about 25–30 bytes *per* minute).

ding the volume of transfused fetal blood which defines massive FMH. Most frequently it is 80 mL and 150 mL of fetal blood in the maternal circulation, estimated to occur with the incidence of 1 : 1,000 to 1 : 5,000 deliveries, respectively [2, 5]. The volume of transfused blood is not the only factor influencing fetal or newborn clinical condition. Numerous factors can contribute to final outcome and long-term prognosis. The most significant among them are chronicity, gestational age, blood group compatibility and possible abdominal trauma. Animal studies revealed that the loss of 30% of total fetal blood volume is better tolerated if it happens within two hours than within 10 minutes [6]. Some authors report no statistically significant difference in long-term outcomes regardless if hemoglobin is higher or less than 60 g/L as well as the volume of transfused fetal blood into maternal circulation is more or less than 200 mL [7]. The chronicity of transfusion process could be the explanation of this finding. Chronic forms of FMH have more benign course than acute, even though the volume of transfused blood is higher, while poor prognosis is expected in acute blood loss. Considering gestational age, preterm infants have a higher risk for adverse outcome [8]. The main reason for this is certainly low adaptation capability to stress in preterm infants caused by FMH. In the context of ABO incompatibility, the maternal coagulation system can be activated which limits hemorrhage. However, if mother and fetus are ABO compatible, there is less possibility that coagulation system would be activated, so more massive FMH could be expected [7]. In the presented case, maternal and fetal blood types were compatible, actually they were both blood type O, Rh-negative, and Coombs test was negative, which according to previous assumption resulted in massive FMH. Other factors associated with FMH are placental abruption, umbilical cord anomalies, amniocentesis and some obstetrical procedures (external cephalic version, manual removal of the placenta) [8].

The clinical presentation of FMH is nonspecific and the literature reports that the most frequent symptoms are reduced or absent fetal movements which were present in the presented case, too [3]. CTG ranges from a sinusoid type over reduced variability with or without later decelerations [9]. The sinusoidal type of the CTG monitoring is typical for fetal anemia or acidosis, and the criteria required for the diagnosis were established by Modanlou and Freeman [10]. Some authors classify sinusoidal type of CTG into three subtypes depending on the oscillation amplitude: minor with the amplitude of 5 to 15 bpm, intermediate with amplitude 16–24 bpm and major with the ampilitude 25 or more bpm, in order to quantify fetal risk [11, 12]. In this case, CTG revealed sinusoidal type with slightly higher oscillation amplitudes of 25 bpm, referring to higher risk of adverse fetal outcome. In cases of massive FMH, transfusion reactions presented as nausea, fever, shiver etc. were described [13, 14]. In our case, the mother was admitted to the hospital isolation unit according to suspicion of viral infection presented with general weakness, mild fever and discrete joint pains, which also correspond to transfusion reaction.

The prenatal diagnostic of FMH is difficult and unreliable, and in most cases occurs in previously normal pregnancies [14]. Mari et al. [15] reported that both mild and severe fetal anemia could be diagnosed by Doppler ultrasound, i.e. by evaluating blood flow velocity through middle cerebral artery (MCA). When fetal anemia occurs, cardiac output and blood velocity increase which can be established by measuring blood flow velocity through MCA. There is an inverted correlation between fatal anemia and the highest flow velocity during systole (peak systolic velocity – PSV) through MCA. Doppler ultrasound evaluation of MCA-PSV is an effective non-invasive method for evaluation of fetal anemia which can be also helpful in making treatment decision: fetal transfusion or delivery, depending on gestational age. Cosmi et al. [16] show that measurement of MCA-PSV is useful in diagnosing fetal anemia caused by chronic fetomaternal hemorrhage. In cases of chronic FMH and sinusoidal fetal heart rate pattern MCA-PSV values greater than 1.5 multiples of the median were observed, while in cases of acute bleeding MCA-PSV were normal. Ultrasound examination can detect changes of biophysical profile manifested with reduction of fetal movements with adequate amount of amniotic fluid [17].

Treatment of choice in proven FMH is immediate delivery in term pregnancy or in a period when adequate maturity of a fetus can be expected. Cesarean section is a desirable mode of delivery, because fetoplacental circulation may be additionally compromised in vaginal delivery. However, in this case, the mother was admitted in the maternity with regular contractions in the expulsion stage with clinical finding refering to the possibility to finish vaginal labor soon. The most frequently applied test for detection of fetal blood in to the maternal circulation is KB test. The estimated volume of transfused fetal blood into maternal circulation was 531 mL in our case. Similar values of 410 mL and 710 mL were reported in other studies too [18, 19]. Such high values, higher than the total fetal blood volume, could be explained with chronic FMT. High reticulocytes count may support the diagnosis of chronic FMT as a sign of compensatory activation of fetal hematopoietic system.

We presented severe FMH in term pregnancy completed soon after admission in the maternity ward with vaginal delivery according to obstetrician finding. The immediately established diagnosis and appropriate and timely therapy resulted in stabilization of infant general condition and good recovery. The newborn was discharged on the day 5 of life without complications. Long-term outcome in such cases with severe acidosis and low hemoglobin level are difficult to predict. Some cases may result in poor outcome, especially if signs of damage were presented on the brain imaging [19]. Magnetic resonance of the brain and the outcome at the age of 6 mouths in the presented patient was normal despite massive FMH and severe anemia and asphyxia at birth.

Regarding the difficulties in the diagnosis of FMH more physician awareness of this condition is of crucial importance [20].

Conclusion

For the successful diagnosis and management of FMH direct communication between the obstetrician and the pediatrician is necessary as presented in this report.

Disclosure

The authors report no conflicts of interest.

R E F E R E N C E S

1. *Ahmed M, Abdullatif M*. Fetomaternal transfusion as a cause of severe fetal anemia causing early neonatal death: A case report. Oman Med J 2011; 26(6): 444−6.
2. *Heise RH, Van Winter JT, Ogburn PL*. Identification of acute transplacental hemorrhage in a low-risk patient as a result of daily counting of fetal movements. Mayo Clin Proc 1993; 68(9): 892−4.
3. *Wylie BJ, D'Alton ME*. Fetomaternal hemorrhage. Obstet Gynecol 2010; 115(5): 1039−51.
4. *Stroustrup A, Plafkin C, Savitz DA*. Impact of physician awareness on diagnosis of fetomaternal hemorrhage. Neonatology 2014; 105(4): 250−5.
5. *Solomonia N, Playforth K, Reynolds EW*. Fetal-Maternal Hemorrhage: A Case and Literature Review. Am J Perinatol Rep 2012; 2(1): 7−14.
6. *Dupont G, Povlsen JV*. Repeated episodes of massive fetomaternal hemorrhage in the same woman. Ugeskr Laeger 1991; 153(39): 2750. (Danish)
7. *Zizka Z, Fait T, Belosovicova H, Haakova L, Mara M, Jirkovska M*, et al. ABO fetomaternal compatibility poses a risk for massive fetomaternaltransplacental hemorrhage. Acta Obstet Gynecol Scand 2008; 87(10): 1011−4.
8. *Stroustrup A, Trasande L*. Demographics, clinical characteristics and outcomes of neonates diagnosed with fetomaternalhaemorrhage. Arch Dis Child Fetal Neonatal Ed 2012; 97(6): 405−10.
9. *Moise KJ*. Diagnosis and management of massive fetomaternal hemorrhage. 2011. Available from: http://www.uptodate.com/contents/diagnosis-and-management-of-massive-fetomaternalhemorrhage [Accessed 2011 July 12].
10. *Modanlou H, Freeman RK*. Sinusoidal fetal heart rate pattern: Its definitionand clinical significance. Am J Obstet Gynecol 1982;142(8): 1033−8.
11. *Murphy KW, Russell V, Collins A, Johnson P*. The prevalence, aetiology and clinical significance of pseudo-sinusoidal fetal heart rate patterns in labour. Br J Obstet Gynaecol 1991; 98(11): 1093−101.
12. *Neesham DE, Umstad MP, Cincotta RB, Johnston DL, McGrath GM*. Pseudo-sinusoidal fetal heartrate pattern and fetal anemia: Case report and review. Aust N Z J Obstet Gynaecol 1993; 33(4): 386−8.
13. *Glasser L, West JH, Hagood RM*. Incompatible fetomaternal transfusion with maternal intravascular lysis. Transfusion 1970; 10(6): 322−5.
14. *Murphy KW, Venkatraman N, Stevens J*. Limitations of ultrasound in the diagnosis of fetomaternal haemorrhage. BJOG 2000; 107(10): 1317−9.
15. *Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ*, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med 2000; 342(1): 9−14.
16. *Cosmi E, Rampon M, Saccardi C, Zanardo V, Litta P*. Middle cerebral artery peak systolic velocity in the diagnosis of fetomaternal hemorrhage. Int J Gynaecol Obstet 2012; 117(2): 128−30.
17. *Tseng L, Didone AM, Cheng C*. Severe anemia in a newborn due to massive fetomaternal hemorrhage: Report of one case. Acta Paediatr Taiwan 2005; 46(5): 305−7.
18. *Willis C, Foreman CS*. Chronic massive fetomaternal hemorrhage: A case report. Obstet Gynecol 1988; 71(3 Pt 2): 459−61.
19. *Kadooka M, Kato H, Kato A, Ihara S, Minakami H, Maruyama Y*. Effect of neonatal hemoglobin concentration on long-term outcome of infants affected by fetomaternal hemorrhage. Early Hum Dev 2014; 90(9): 431−4.
20. *Kuin R, Rosier-Dunné FM, Plötz FB*. Shock management in acute fetomaternal hemorrhage. J Matern Fetal Neonatal Med 2013; 26(11): 1151−2.

Received on June 5, 2015.
Revised on July 28, 2015.
Accepted on August 4, 2015.
Online First May, 2016.