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Massive feto-maternal transfusion: A literature review and case report

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Abstract

Objective: Massive Fetomaternal Hemorrhage (FMH) is an obstetrics emergency. To date, etiology remains unknown. The signs and symptoms are unfortunately unspecific and often the suspicion for the diagnosis arises when the neonatal outcomes are unfavorable. The aim of our work is to raise awareness on this topic and to identify correct obstetric management in order to promptly identify the condition and avoid possible fatal consequences.

Methods: The search was conducted by means of the PubMed, Google Scholar, Cochrane databases. There was no limitation set on the date of publication. We also report a case of massive FMH arising in a full term pregnancy.

Results: Reduced or absent perception of fetal movements, CardioTocoGraphic (CTG) anomalies, ultrasound signs of fetal hydrops and increase in the systolic speed peak in the middle cerebral artery (MCA-PVS) are strongly suggestive signs of FMH. In these cases it is necessary to perform an urgent cesarean section followed by careful resuscitation, in order to minimize the consequences of massive anemia on neonatal outcomes. In any case, the Kleihauer-Betke (KB) test, demonstrating the substantial presence of fetal blood in the maternal circulation, is fundamental for the diagnosis.

Conclusion: Currently there are a small number of cases in the literature and there are no guidelines on the management. The purpose of this article is to focus the attention on this rare obstetric complication and try to provide a valid management through an illustrative case and a review of the literature.

Keywords

Fetomaternal Hemorrhage; Fetomaternal Transfusion; 'Fetal Anemia; 'Pregnancy care; Neonatal outcomes.

Abbreviations

FMH: Feto-Maternal Hemorrhage; MCA-PSV: Peak Systolic Velocity in the Middle Cerebral Arteries; KB: Kleihauer-Betke; G2P1: Gravida 2 Para 1; CTG: Cardiotocography; NAIT: Neonatal AlloImmune Thrombocytopenia; HE: Hemoglobin Electrophoresis; STV: Short Term Variation; RC: Reticulocyte; RBCs: Red Blood Cells ; IUT: Intrauterine Transfusions; MCHC: Mean Corpuscular Hemoglobin Concentration; PIMCA: middle cerebral artery pulsatility index ; PIUA: umbilical artery pulsatility index.

Introduction

Feto-Maternal Hemorrhage (FMH) is defined as a substantial loss of fetal blood in the maternal circulation. During the pregnancy, the placenta normally prevents the transfer of cells between fetus and mother and vice versa, in order to maintain separate the two circulations. Nevertheless, in a majority of pregnancies and in particular during delivery, a small portion of fetal erythrocytes (<0.1 ml) can be found in maternal circulation, without any negative effects on the newborn [1]. Car et al., in a recent analysis, estimated that up to 40% diagnosis of severe FMH was missed. [2]

Currently, there is no universal definition of FMH. Renaer et al. defined macro transfusion when more than 10 mL of fetal blood are found in the maternal circulation, because it is the threshold from which the blood passage is neutralized by 100 mg of anti-D immunoglobulin [3]. Instead, Almeida et al. consider a higher threshold (80 mL), beyond which neonatal anemia becomes evident [4]. Therefore, the frequency of FMH, depending on the threshold considered, varies from 1 to 5 cases for every 1000 births, with an approximately prevalence of 3-5% among unexplained fetal deaths [5]. However, in about 0.3% of pregnancies, the volume of FMH exceeds 30 mL, which roughly corresponds to 10% of blood volume in a 3 kg newborn, assuming that the estimated blood volume of a neonate is 85 to 100 mL/kg [6]. FMH, with volume of fetal blood up 50 to 60 mL, can cause life-threatening complications such as neonatal hypovolemic shock, anemia, hydrops, respiratory distress or even fetal loss [7]. It is also associated with a 40% to 50% perinatal mortality and with a significant risk of neurological sequelae among survivors [4,8].

An important distinction is between acute and chronic forms of FMH, because not much of the quantity but the duration of the bleeding is determinant for the neonatal outcomes [9].

Most of the time FMH occurs spontaneously in uncomplicated near term pregnancies, without apparent trigger factors. The etiology of this obstetric complication remained unknown in 82% of cases [10]. The American College of Obstetricians and Gynecologists identified the main risk factors for a severe FMH represented by antepartum death, cesarean section, abruptio placentae, placenta previa, manual removal of the placenta, intrapartum manipulation and antepartum bleeding [11].

Unfortunately, prenatal recognition is extremely rare and in almost all cases it may become apparent only after injury has occurred. Indeed in most cases it runs asymptomatically, except for nonspecific symptoms. A classical triad, described in literature as a late manifestation of fetal anemia, includes decreased perception of fetal movements, abnormal cardiotocography (more often represented by sinusoidal fetal heart rate pattern) and hydrops fetalis [12]. More recently, the focus has been on Peak Systolic Velocity

in the Middle Cerebral Arteries (MCA-PSV), detected by Doppler ultrasound suggesting a possible role of a peak speed increase in predicting severe FMH [13-15]. The most common test for the detection of fetal red blood cells in the maternal circulation is the Kleihauer-Betke (KB) stain.

Currently, in literature there are many case reports and few retrospective studies that describe pregnancies complicated by FMH but, especially in idiopathic cases, there are still no specific guidelines to minimize serious consequences of these rare obstetric complications.

The aim of our review is to identify, through the study of existing literature, the main risk factors and clinical-laboratory signs in order to immediately identify a fetal-maternal transfusion and set up a correct management to avoid unrecoverable fetal sequelae. We also report a case of severe FMH occurring in the third trimester of an apparently normal pregnancy.

Material and Methods

The search was conducted by means of the PubMed, Google Scholar, Cochrane databases and updated until March 2022. There was no limitation set on the date of publication. The keywords used for the search were: ''Fetomaternal Hemorrhage'' or ''Fetomaternal Transfusion'', ''Fetal Anemia'' or "Massive Fetal Hemorrhage". Based on these terms, case reports, review articles and original articles of interest were analyzed with regard to FMH in pregnancy. We have excluded non-English language studies from our search.

Case Presentation

A 32-year-old female, G2P1, blood type A positive, was admitted at 36 weeks and 1 day of gestation because of decreased fetal movements perception in the last 36 hours. No history of pain, trauma or vaginal bleeding are reported. The patient denied other pathologies, including a recent history of viral illness. She reported no smoking habitude and denied drug or alcohol abuse. Pregnancy history was unremarkable, with normal first and second trimester screenings, normal estimated birth weight and Doppler velocimetry. Past obstetric history revealed a normal delivery at term. On arrival the office-sonography revealed a live fetus of normal size for gestation with few movements and normal amniotic fluid volume. Cardiotocography (CTG), performed for 30 minutes, revealed a reduced beat to beat variability with two little variable decelerations and none accelerations (Figure 1). In consideration of the absence of fetal movements and the abnormality of the cardiotocographic tracing, an emergency cesarean section was performed. A 3100-gram female infant was delivered. Apgar scores were 0/0/1, reported within 1, 5 and 15 minutes of life respectively. The infant appeared floppy and markedly pale at birth. She presented respiratory depression, not responding to bag and mask ventilation. Plasma expanders were administered and she was resuscitated for 20 minutes, without any improvement in clinical condition. The electroencephalogram confirmed neonatal death. The arterial cord blood gas revealed a pH of 6.80, HCO_3 of 16.1 mmol/L, base deficit of 18.1 mmol/L, glycemia of 4 mg/dL and lactate of 17 mmol/L. Neonatal hemoglobin was 2,5 g/dl. The KB test, done on the mother's blood, revealed the presence of 5.88% of fetal blood in the maternal circulation, which is nearly 130 ml of fetal blood. This confirms the diagnosis of a severe FMH, reaching up to 45 ml/kg of fetal blood. Macroscopically the placenta appears diffusely pale with cicatricial areas with a max diame-

ter of 1.5 cm. The histological examination highlighted the presence of nucleated red blood cells in the villar bloodstream and marked anemia of the intervillary spaces in absence of phlogistic aspects. The maturity of the villi appeared in accordance with the reported gestational period. The autopsy showed cerebral edema, hepatomegaly, pleural and pericardial effusion without evidence of organ damage, as for acute onset of hemorrhagic shock.

Discussion

Massive FMH was described for the first time by Wiener in 1948 and pathophysiology is still uncertain [16]. Several theories have been proposed to explain the transfer of fetal blood cells through the placenta. A disruption of the uteroplacental interphase, resulting from inflammatory or mechanical factors, is realistically thought to be the cause of this life-threatening complication [17]. According to Wentworth et al, the uterine contractions during the third trimester of pregnancy could create small areas of capillary damage in the placenta allowing the passage of small portions of fetal erythrocytes in the maternal circulation [18].

Other factors predisposing FMH >30 mL has been identified in abdominal trauma [19], external cephalic version [20], amniocentesis [21], chorionic villus sampling, manual removal of the placenta [22], abruptio placentae [23], placental tumors such as chorioangiomas and uterine choriocarcinomas [24,25], preeclampsia [19], monoamniotic monochorionic twins [26].

In the diagnostic evaluation, at first they must always be investigated viral infection, specifically parvovirus, VDRL reactivity, Neonatal AlloImmune Thrombocytopenia (NAIT), feto-maternal blood incompatibility and Coombs test negativity, which are the most frequent causes of FMH.

Nevertheless, in most cases (up to 82%) any triggering factor could be observed and the etiology of FMH remains unknown. Giacoia et al, in his review, reported 134 cases with FMH greater than 50 mL, of these 111 cases in absence of an antecedent precipitating event [27]. This data was further confirmed by Kecseks et al retrospective analysis which identified a risk factor for FMH in 2 of 16 considered cases [13].

Antenatal diagnosis is rare and very difficult because of the unspecificity of signs and symptoms. The classical triad described in literature is represented by decreased fetal movements perceptions, abnormal/sinusoidal heart rate pattern and hydrops fetalis [13,27]. These signs, though rarely occurring and not always in association to adverse outcomes, should lead to strong clinical suspicion of FMH.

A reduction of fetal movements represents a compensation mechanism adopted by the fetus in order to reduce energy consumption, preserve oxygen reserve and shunt it towards brain, heart and adrenal glands [28]. Decreased or absent fetal movement was reported by 27% of mothers reviewed by Giacoia et al and 54% of those of Christensen et al [7,27]. Therefore, it can be useful to train the mother in counting fetal movements.

As regards the CTG findings, a sinusoidal pattern is considered a pathognomonic sign of fetal anemia. It was first described by Modanlou et al and Freeman et al in 1982 as a rate of 120 to 160 beats/min,

no reactivity, fixed or flat short-term variability and oscillation of the sinusoidal waveform above and below the baseline [29]. However, this pattern is not always observed. Giacoia et al noticed that a sinusoidal fetal heart rate pattern occurred in only approximately 10% of FMH cases [27]. Even in our case a sinusoidal CTG pattern was not detectable, although it showed a reduced beat to beat variability with variable decelerations and absence of accelerations. A significant reduction of Short Term Variation (STV) is highly associated with fetal acidaemia, which occurs in massive FMH. However the use of a computerized CTG is more appropriate than standard [30].

Hydrops fetalis consists of a generalized accumulation of fluid, or edema, in at least two fetal compartments, firstly described by Ballantyne et al in 1892. The main causes of this condition are fetal anemia (distincted in immune or non-immune), hypoproteinemia and cardiac failure. In case of FMH the anemia is secondary to a fetal bleeding in the maternal circulation, resulting in a non-immune hydrops [31].

Recent studies have shown how an increase in the fetal middle cerebral artery peak systolic velocity MCA-PSV, detected by Doppler ultrasound, could be an important parameter for the diagnosis of fetal anemia [32-34,15]. Its role in predicting FMH is still uncertain, but promises to aid in the diagnosis of this elusive and potentially fatal obstetric complication [16].

An important distinction is between acute and chronic FMH, both as regard diagnosis and case management. In fact a large loss of blood during a prolonged period is well-tolerated by the fetus compared to a smaller acute blood loss. In chronic forms the fetus has time to activate functional compensatory mechanisms such as hematopoiesis or intravascular volume regulation, which cannot be activated if blood loss occurs acutely [8,35].

Hematologic indices at birth suggest information regarding the duration of the bleeding. In particular it is important to evaluate the Reticulocyte (RC) and nucleated Red Blood Cells (RBCs) count in the peripheral circulation. RC at birth normally varies from 3% to 7%, so it can be considered 7% as a cut-off to distinguish acute or chronic FMH. A RC count major than 7% and a very high RBCs count at birth suggests bone marrow hyperactivity for at least 3-4 days (the RC appear after 72 hours in the peripheral blood) and so indicate a long duration of bleeding. Also a low Mean Corpuscular Hemoglobin Concentration (MCHC) in these infants suggests chronic blood loss, resulting in neonatal anemia. The MCHC parameters have a prognostic importance about the possibility of developing significant anemia during the childhood, therefore these infants have to be closely followed. Conversely, a normal RC count and a mild increase in nucleated RBCs at birth are oriented towards a diagnosis of acute FMH [10].

The clinical presentation of these infants appears very differently. Infants with chronic FMH are euvolemic, not acidotic and not required aggressive resuscitation at birth [36]. In reverse, infants with acute FMH present an important metabolic acidosis with higher base deficit, low Apgar score and hypotension requiring a prompt resuscitation with an equivalent amount of saline or packed RBCs to restore their volume status [10].

The most common test used to confirm the FMH diagnosis by detecting fetal red blood cells in the

maternal circulation is the KB stain, first described by Kleihauer et al in 1957. It consists in the exposure of a mother's blood smear to an acid bath that removes adult, but not fetal, hemoglobine from the red blood cells. After exposure to acid, the maternal cells appear ghost-like and the fetal cells, still containing fetal hemoglobin, are identified as pink cells and counted in a peripheral smear [37]. However the KB test could be influenced by numerous factors such as temperature, pH, time, number of cells counted, thickness of the smear, hereditary persistence of fetal hemoglobin, sickle-cell anemia, beta thalassemia trait, half-life of reagents and subjective interpretation [38].

An alternative diagnostic method is the Flow Cytometry that determines the number of fetal erythrocytes in a maternal venous blood sample exploiting monoclonal antibodies binding the fetal hemoglobin [39]. This technique compared with the KB test appears faster and ensures a major objectivity of interpretation and a better accuracy. Nevertheless, the major cost and the limited availability of experienced laboratory technicians limit its use to a few hospitals [35]. A new auxiliary tool to diagnose FMH when KB test or Flow Cytometry are not available was recently proposed by Stanic et al 2020. Indeed, in two cases of suspected FMH, they tried to diagnose abnormally elevated concentrations of HbF in the mother's circulation using the Hemoglobin Electrophoresis (HE) method [40]. Tao et al. in a recent single center observational study suggest the idea that maternal alpha-fetoprotein (AFP) testing is valuable to confirm massive feto-maternal hemorrhage [41]. In fact, due to FMH, the maternal alpha-fetoprotein value increases significantly and can therefore be used as a marker.

Anyway, in case of unexplained feto-neonatal anemia or death, FMH should always be excluded as a possible cause and long-lasting persistence of fetal blood cells in the maternal circulation, offers the opportunity to diagnose FMH also at a later date [42].

The management of FMH varies according to gestational age, estimated amount and duration of hemorrhage and fetus' stability. In the early third trimester of gestation, but also in a very premature fetus (<28 weeks gestation) who has evidence of a chronic massive FMH (severe anemia, normal results of blood gas indices, sinusoidal CTG pattern and hydrops) serial Intrauterine Transfusions (IUT) could be performed [43]. Instead, in a low grade FMH a wait-and-see management was possible, following the fetal well-being through CTG monitoring to evaluate fetal heart variability, serial KB test to determine how FMH is evolving and ultrasound examinations to evaluate hydrops, fetal growth and MCA-PSV [44].

However in almost all cases an antenatal diagnosis of massive FMH is difficult. In these cases the therapeutic goal is a prompt delivery followed by an appropriate fluid resuscitation to restore an adequate volume and transfusion therapy to correct the anemia.

Recently, Ficarola et al. proposed a standardized algorithm and management protocol in order to reduce the time of the diagnosis in case of reduced fetal movements and suspected FMH. It includes an immediate ultrasound evaluation of fetal heartbeat and placenta and amniotic fluid. Then they suggest assessment of obstetric risk factors and performance of 20-50 minutes of NST. The subsequent steps of the algorithm depend on gestational age, NST reactivity and pattern and include: assessment of amniotic fluid, estimated fetal weight and possibly a growth restriction, umbilical artery (PIUA) and middle cerebral

artery pulsatility index (PIMCA), assessment of fetal movements, MCA-SV monitoring [45].

In a full-term infant the initial volume replacement should be obtained rapidly, over 10-15 minutes in order to avoid a prolonged tissue underperfusion. Instead, in the premature neonates a rapid volume restoration is dangerous, since a sudden rise in systemic pressure can damage capillaries and result in intracranial hemorrhage and/or pulmonary edema. The first choice treatment for volume replacement is a transfusion of uncrossed matched 0 negative whole blood. An alternative is the administration of plasma expanders (5% albumin, fresh frozen plasma, normal saline, or Ringer's Lactate). An alternative therapeutic choice to consider for prompt correction of severe anemia when there is not a hypovolemic state is exchange transfusion [46]. Also a respiratory support by mechanical and supplemental oxygen is necessary. Subsequently the treatment aim is to sustain a circulatory system. It could be necessary to administer positive inotropic agents like dopamine, dobutamine and epinephrine, or corticosteroids in case of refractory hypotension. It's important to consider that in acute hemorrhage the hemoglobin value at birth doesn't reflect the real degree of bleeding, because the hemodilution occurs only several hours later [47].

The rate of stillbirth was 15% to 25%, neonatal death rate was 8% to 38% [5,11]. It has been observed that a significant portion of survivors developed adverse neurological outcomes (4% to 18%) including intravascular hemorrhage, cerebral infarction, ventriculomegaly, periventricular leukomalacia, cerebral atrophy [9,27] and that infants with normal initial neurological examinations could develop cerebral palsy. Approximately 20-30% of affected neonates present one or more of these outcomes [35,48]. It depends on various factors among which the most important are gestational age, quantity and rapidity of fetal blood loss. According to Kecskes et al the main predictors of an adverse outcome in neonates with large FMH are the postnatal presentation and an initial hemoglobin level lower than 4g/dL [13].

Conclusion

Our work describes a case of acute, massive FMH at 36 weeks gestation and subsequent devastating neonatal complications, hesitating in neonatal death.

Massive FMH is a rare life-threatening obstetric complication with a high risk of adverse neonatal outcomes. The etiology is unknown and the absence of clear signs and symptoms makes its prenatal diagnosis very difficult. A reduced or absent perception of fetal movements associated with fetal heart rate abnormalities must lead to a strong suspicion of FMH. In these cases it is necessary to perform an urgent delivery and prompt resuscitation of the newborn in order to prevent possible fatal outcomes.

Currently there are a relatively small number of cases in the literature and there are no guidelines on the management of this rare occurrence. The purpose of this article is to focus the attention on this rare obstetric complication and try to provide a valid diagnostic and management strategy through an illustrative case and a review of the literature.

Declarations

Conflicting interests: The authors declare that they have no conflicts of interest and nothing to disclose.

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