An unusual case of rapidly progressive hemolytic anemia in the late preterm period: case report and literature review

Summary
Rh isoimmunization is the main risk factor for fetal anemia. In moderate to severe cases, intrauterine transfusion before 34 weeks and delivery after 37 weeks, are the accepted treatments. However, in the late preterm period, there is no consensus on the accepted course of action. We report a case of Rh isoimmunization with rapidly progressive fetal anemia at 35 weeks of gestational age that was not detected by Doppler ultrasound. We discuss the optimal management in this gestational period according to the current literature.

Keywords: Rh isoimmunization, fetal anemia, intrauterine transfusion, doppler

Introduction
Although Rh isoimmunization hemolytic anemia has been virtually eradicated of developed countries due to an effective primary prevention, in developing countries it still represents a serious problem. Fourteen percent of Rh (-) women will develop antibodies during the first 6 months postpartum or during the next Rh (+) pregnancy. Every year, more than 350 000 cases occur worldwide, of which 33% will need treatment; 14% will have intrauterine death; 24% will die in the neonatal period (from kermietis, hydrops fetalis and associated problems); and 29% will develop severe hyperbilirubinemia (more severe than jaundice due to other causes), with risk of potentially irreversible neurological damage.

The anemia compensatory mechanisms include increasing cardiac output and hyperdynamic circulation. However, if the hepatic, splenic, bone marrow and extramedullary (skin, placenta) erythropoiesis do not compensate for the hemolysis, hydropsfetalis (advanced expression of cardiac failure) develops and intrauterine death can occur. Strict monitoring is mandatory, since, even intrauterine transfusion (IUT) can suppress erythropoiesis and cause late onset severe anemia. Furthermore, the survivors can develop medium and long term complications including heart function and morphology alterations or cerebellar lesions, especially in fetuses between 24-32 weeks.

The early detection of anemia severity improves prognosis. This has good correlation with Doppler measurement of middle cerebral artery peak systolic velocity (MCA-PSV) due to cerebral vasodilation secondary to hypoxia, but mainly to a reduced viscosity due to low hematocrit. This noninvasive method has replaced anmiocentesis. A value of 1.5 times the median (MoM), is considered indicative of severe fetal anemia and intrauterine transfusion should be considered if diagnosis is confirmed with fetal blood sampling.

Case report
29 year old pregnant woman (34 6/7 weeks by 1st trimester ultrasound), with adequate prenatal care, G3P2002, G2 C-section in 2014, with infant with neurological dysfunction secondary to Rh isoimmunization anemia; comes to the emergency room of Alberto Sabogal Sologuren National Hospital on Feb 1st, 2017 for ultrasound monitoring due to finding of positive indirect Coombs 1/1512 (Dec 19th, 2016). She had MCA-PSV: 57m/s (Figure 1), a cardiotocographic monitoring was considered reactive (Figure 2), and weekly ambulatory monitoring was recommended. She returned on the following day, with sporadic uterine contractions and “because she did not feel right about her fetal well-being”. The physical exam was non-contributory, without contractions or cervical changes. The fetus had a heart rate of 140beats per minute, 2760 grams of weight (54th percentile), middle cerebral artery pulsatility index MCA PI= 1.69 (>5th centile); umbilical artery pulsatility index = 0.8 (< 95th centile) and MCA-PSV =70, 72, 73m/s (three consecutive measurements equivalent to 1.43 MoM corresponding to mild anemia, Figure 3).

After informed consent, cordocentesis for fetal blood sampling was done, with free hand technique, at cordon insertion site in the placenta with 21G needle, with success in the first attempt. 5ml of umbilical blood from vein was obtained, discarding the first 2ml to reduces the risk of maternal contamination and sample was sent for hematocrit, blood type and direct Coombs, 3, 10 The results were Hb: 7.7g/dL, O Rh(+) and positive respectively. It was decided to perform a C-section with delivery of a female product of 2702grams, Apgar 9/9, neonatal hemoglobin 7.9 and 7g/dL, total bilirubin 6.8 and 10.71mg/dL (4 and 7 hours post-delivery respectively). She was admitted to neonatal ICU where exchange transfusion was performed twice for recurrent anemia. Phototherapy was done during 5 days, and bronchiolitis treatment was required with good evolution and discharge at 25 days.
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We report a case of fetal anemia due to Rh isoimmunization at 35 weeks of gestational age whose rapid progression was evidenced by the worsening of the MCA-PSV, in which case, despite the fact that the last ultrasound measurement indicated mild anemia, a cordocentesis was ordered due to the increased speed flow of the MCA, the history of neurological compromise in the prior pregnancy and to the elevated MCA-PSV value-, to decide about performing a cordocentesis, as well as the presence of hydrops, high antibody titer or high clinical suspicion, due to the presence of many reports that indicate that the anemia is more severe, and starts 8-10 weeks earlier than in prior pregnancy, in pregnant woman with history of isoimmunization. For example, in a case series, 5 of 35 fetuses with severe anemia, would have been missed if only the MCA-PSV was considered to decide to perform a cordocentesis. In our case, the hemolytic component had a rapid progression, worsening within hours, including the neonatal period. This evolution is explained by the fact that the hemolysis does not resolve with delivery and that the disease remains active due to the cytotoxic and humoral activity, and this behavior can persist until it requires exchange transfusion. Therefore, in this case, our decision for blood sampling was based in the understanding of the dynamic behavior of the hemolytic problem (the tendency to the increment of the disease in the prior pregnancy) more than in a single ultrasound value. In fact, the main idea of this case report is based on the understanding that the obstetric problems are dynamic, and in this case, the hemolytic behavior could not be considered only on the basis of a MCA-PSV value, but instead, other factors needed to be taken into account to diagnose fetal anemia. High clinical suspicion should always be considered, to avoid adverse events, because, without doing cordocentesis, in this case, the patient would have been scheduled for follow up in 1 week, with unsuspected consequences.

On the other hand, the goals of intrauterine transfusion (IUT) are to avoid prematurity and the delivery of a neonate without or with only mild anemia. The preterm metabolizes bilirubin inefficiently (due to the increased production for the large number of senescent erythrocytes, lower liver uptake, deficient conjugation and to the increment of B-glucuronidase activity with subsequent enteric reabsorption). In fact, the indication of phototherapy is lower in neonates that receive IUT. Consequently, there are studies that support the invasive approach between 34 and 37 weeks. For example, Pasman reported 135 IUT performed between 2000 and 2014 in the University Hospital of Leuven, with 19 successful procedures performed in >34 weeks (with exception of a case with a mild event) without fetal-neonatal death. With this good experience, this group recommends performing IUT until 36 weeks and plan delivery starting at 37 weeks. However, a Finnish study, with 339 transfusions done between 2003-2012 reported 11 cases of severe fetal bradycardia that required emergent C-section (6 in >34 weeks, that fortunately survived). Even more, a study in Stockholm with 284 IUT did between 1990-2010, reported complications in 14 procedures. From these, 3 occurred in ≥ 34 weeks, with one case of transfusion at 36 weeks and intrauterine death at 37 weeks. Likewise, Klumper, found 9 neonatal deaths in 609 procedures, 4 of which had more than 34 weeks, two with hydrops (which confers worse prognosis), and two that died after delivery, within 24 hours post procedure, who, according to the authors, would have benefited with a delivery.

Based on these experiences, we can say that, to decide an IUT in a pregnancy ≥ 34 weeks, we need to balance the risks and benefits of the procedure, with those of a premature delivery and morbidity of anemia and hyperbilirubinemia. This decision should be made based on a high clinical suspicion, according to prior studies and to the technical expertise available. Some experts recommend to do it if there are favorable conditions, as is the case with anterior placenta, technical expertise available. Some experts recommend to do it if the patient is obese, or if only a free loop is accessible, it is preferable to choose a delivery. But, in general, the expert opinion is that IUT should be performed only until 35 weeks, because after this time, the risks of IUT exceed those of the delivery.

Conclusion

In summary, we can conclude:

a. Cordocentesis maintains its role for fetal blood sampling to diagnose anemia and its performance, if needed, should not be delayed.

b. Hemolytic anemia due to Rh isoimmunization can have a rapidly progressive behavior, and the management based in VSP-ACM, according to the clinical context, should be done based on the tendency of the speed, more than based on a single value.

c. The decision to do an intrauterine transfusion or deliveralate preterm product should be done in an individualized manner, considering the risks and benefits of both decisions, but, in accordance to the expert opinion the IUT should not be performed after 35 weeks.

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Conflict of interest

The authors declare that they have no conflict of interest.

References


