SYMPOSIUM FETAL SURGERY IN LATIN AMERICAN COUNTRIES

1. Clínica Delgado Auna, Lima, Peru.
2. Peruvian Institute of Fetal Medicine and Surgery, Lima, Peru.
   a. Fetal Surgery - Fetal Medicine, ORCID 0000-0001-6515-2599
   b. Fetal Medicine ORCID 0000-0002-6700-4925
   c. Anesthesiology ORCID 0000-0002-0202-0676
   d. Blood Bank ORCID 0000-0001-9602-1081
   e. Neonatology ORCID 0009-0003-2925-6683
   f. ORCID 0000-0002-2709-0312
   g. ORCID 0000-0001-7088-5877

Conflict of interest: The authors declare that they have no conflict of interest.

Funding: None.

Received: 5 March 2024

Accepted: 6 March 2024

Online publication: 30 March 2024

Corresponding author:
Dr. Enrique Gil Guevara
Calle Las Colinas 190, Lima, Perú. CP: 15023
enrique.gil@doctors.org.uk

Cite as: Gil Guevara E, Diez Chang G, Miranda Frisancho B, Pérez I, Bazán C, Muñoz Acosta J, Gonzales Carrillo O. Intracardiac fetal therapy: report of the first successful fetal cardiac intervention in Peru, with postnatal correlation at birth and 18 months of life. Rev peru ginecol obstet. 2024;70(1). DOI: https://doi.org/10.31403/rpgo.v70i2607

Intracardiac fetal therapy: report of the first successful fetal cardiac intervention in Peru, with postnatal correlation at birth and at 18 months of life

Terapia fetal intracardiaca: comunicación de la primera intervención cardiaca fetal exitosa en el Perú, con correlación posnatal al nacimiento y a los 18 meses de vida

Enrique Gil Guevara[1,2,a], Guillermo Diez Chang[1,b], Braowell Miranda Frisancho[1,c], Ina Pérez[1,d], Carlos Bazán[1,e], Jairo Muñoz Acosta[2,f], Oswaldo Gonzales Carrillo[2,b,g]

DOI: https://doi.org/10.31403/rpgo.v70i2607

ABSTRACT

Fetal anemia is a cause of perinatal morbidity and mortality. Although it has different etiologies and despite the introduction of RhD immunoglobulin prophylaxis, alloimmunization remains one of its main causes. These pregnancies are initially identified by measuring in the fetus the middle cerebral artery peak systolic velocity (MCA-PSV) and moderate to severe anemia should be suspected when the MCA-PSV is ≥1.50 multiples of the median. In these cases, the actual hematocrit is determined by obtaining fetal blood. Intervention with a fetal hemoglobin no lower than 7g/dL results in a better fetal outcome compared to waiting until the development of severe anemia <5g/dL or hydrops. Intravascular fetal transfusion is preferable to intraperitoneal transfusion due to higher survival rates, particularly of hydropic fetuses. The umbilical vein is the preferred vascular site due to ease of access and greater safety compared to other vascular sites. Direct cardiac puncture is rarely performed because of an increased risk of serious complications, including fetal death. In the present article we present the first case reported in our country of intracardiac transfusion in a fetus with severe anemia due to Rh isoimmunization, which had an exhaustive and difficult management, but with an excellent subsequent fetal, neonatal and postnatal evolution.

Key words: Anemia, fetal, Rh isoimmunization, Fetal heart intervention, Blood transfusion, intracardiac

RESUMEN

La anemia fetal es una causa de morbilidad y mortalidad perinatal. Aunque tiene diferentes etiologías y a pesar de la introducción de la profilaxis de inmunoglobulina RhD, la aloinmunización sigue siendo una de sus principales causas. Estos embarazos se identifican inicialmente midiendo en el feto la velocidad sistólica máxima de la arteria cerebral media (MCA-PSV) y se debe sospechar de anemia moderada a grave cuando el MCA-PSV es ≥1,50 múltiplos de la mediana. En estos casos, el hematocrito real se determina obteniendo sangre fetal. La intervención con una hemoglobina fetal no menor a 7 g/dL resulta en un mejor resultado fetal en comparación a esperar hasta el desarrollo de anemia grave < a 5 g/dL o *hidrops*. La transfusión fetal intravascular es preferible a la transfusión intraperitoneal debido a mayores tasas de supervivencia, particularmente de fetos hidrópicos. La vena umbilical es el sitio vascular preferido debido a la facilidad de acceso y una mayor seguridad en comparación con otros sitios vasculares. La punción cardíaca directa rara vez se realiza debido a un mayor riesgo de complicaciones graves, incluida la muerte fetal. En el presente artículo presentamos el primer caso comunicado en nuestro medio de transfusión intracardiaca en un feto con anemia severa por isoinmunización Rh, el cual tuvo un manejo exhaustivo y difícil, pero con una excelente evolución fetal, neonatal y posnatal.

Palabras clave. Anemia fetal, Isoinmunización Rh, Corazón fetal, intervención, Transfusión sanguínea, intracardiaca

Introduction

Cases of hemolytic disease of the fetus and newborn have been described since the years of Hippocrates. In 1932, Diamond described the neonatal disease as erythroblastosis fetalis[1] and Levine, in 1941, demonstrated the causal relationship between anti-RhD antibodies and hemolytic disease[2]. The immune causes are related to alloimmunization following maternal exposure to fetal red blood cell antigens, forming maternal antibodies and fetal hemolysis. There are more than 50 antigens associated with fetal hemolysis; however, severe fetal anemia is related to Rhesus (Rh)D, Rhc or Kell type alloimmunization[3,4].

Attempts at intrauterine management are attributed to Bevis in England and Liley in New Zealand. Both analyzed the bilirubin content in amniotic fluid to determine the possibility of imminent fetal death due to hemolytic anemia[5,6]. Likewise, Bevis attempted the first fetal transfusion by injecting blood directly into the placenta, with discouraging results. Liley is credited with the first successful intraperitoneal transfusion with a 34-week newborn after two intraperitoneal transfusions[7].

In 1981, Rodeck reported the first successful intravascular transfusion, with the use of a fetoscope into the placental insertion of the umbilical vein[8]. And Bang, in 1982, performed the first ultrasound-guided intravascular transfusion into the intrahepatic portion of the umbilical vein[9]. Later publications mention that access to the intrahepatic portion of the umbilical vein for fetal blood sampling or transfusions was the safest[10], and that the use of fetal paralytic agents helped to improve the success of the procedure[4]. These important advances helped to improve neonatal survival, between 80 and 90%[11].

One of the first publications on the use of intracardiac transfusion was by Westgren et al. in 1998[12]. The researchers concluded that, despite the complications in this type of procedure, intracardiac transfusion is feasible when the intravascular route is difficult to access.

Methodology

An analytical cross-sectional time series study was carried out to obtain recorded data on intrauterine blood transfusions, especially fetal intracardiac transfusions.

In the present article we present the first case in our environment of intracardiac transfusion in a fetus with severe anemia due to Rh isoimmunization, which had an exhaustive and difficult management, but with an excellent fetal, neonatal and postnatal evolution (Figure 1).

Clinical case

A 38-year-old female patient was admitted to the clinical center from Ecuador with a gestation of 25 weeks 3 days and a diagnosis of Rh isoimmunization. She had a history of two children born by cesarean section; the last one had hemolytic anemia and neonatal jaundice despite the application of the anti-D vaccine.

In the current pregnancy, the fetus was observed with severe ascites and pericardial effusion during the ultrasound evaluation. Immunohematological study was requested from the mother, which revealed blood group A, Rh factor negative, phenotypes C-, E-, c+, e+, K-, k+, Kpa-, Kpb+, Fya+, Fyb+, Jka-, Jkb+, Lea-, Leb+, S+, s+, M+, N-, P1+, Lua-, Lub+. Anti-D antibody tracing was 1/256.

Figure 1. Multidisciplinary team in fetal cardiac blood transfusion (fetal surgeon, fetal physician, hematologist, anesthesiologist).

After the evaluations and after the fetus was classified as having hydrops fetalis due to severe anemia due to Rh isoimmunization and fetal bradycardia, the severity of the clinical picture and the need for an emergency fetal blood transfusion were explained to the parents.

The first blood transfusion was scheduled 48 hours after the first evaluation. Prior to the procedure, difficulty in approaching the umbilical vein at the placental level and free loop was observed by ultrasound evaluation, due to the large increase in placental volume (placentomegaly) secondary to severe fetal anemia. It was decided to perform the transfusion by cardiocentesis at the level of the right ventricle, using a 21-gauge needle 15 centimeters long. After insertion of the needle into the fetal heart, 0.5 milliliters (mL) of blood were obtained for hemoglobin (Hb) analysis and blood group study. The fetal Hb reading was 3.5 g/dL.

We proceeded to transfuse 39 mL of fresh, leukoreduced, irradiated, washed, and concentrated O (-) globular packet with 80% hematocrit. The post-transfusion Hb was 11.6 mg/dL. The fetal blood group detected in the blood sample was A (+). The procedure was performed without complications and discharge was decided the following day, with indication of micronized progesterone vaginally.

Ultrasound monitoring 3 days after the procedure revealed a 25-week 6-day-old female fetus weighing 1,127 grams, with subcutaneous edema, fetal ascites, pericardial effusion, increased amniotic fluid volume and enlarged placenta. Cardiomegaly and tricuspid reflux were also observed. The pulsatility index of the different vessels evaluated by Doppler ultrasound was preserved and the peak systolic velocity (PSV) of the middle cerebral artery (MCA) was 57.7 cm/sec (greater than 1.5 multiples of the median (MoM)). A new transfusion was decided 8 days after the first procedure.

The second and third transfusions were performed at 26 weeks 4 days and 30 weeks of gestation, respectively, via the transplacental route through the umbilical vein, without complications. Weekly ultrasound evaluations showed an evident fetal improvement, with a decrease in ascites and pericardial effusion. The fetal Doppler was in adequate values and the VPS ACM was below 1.5 MoM.

It was decided to hold a medical meeting at the gestational age of 33 weeks 2 days to determine the subsequent management of the case, considering the 3 blood transfusions performed, one of them by cardiocentesis, with good fetal evolution. In addition, there was a history of two previous cesarean sections. It was decided to schedule a fourth intrauterine transfusion at 34 weeks 0 days, whose objective was to leave a post-transfusion Hb of 16 g/dL and to schedule the end of gestation at 36 weeks, previously applying a complete course of pulmonary maturation prior to the intrauterine transfusion.

The fourth fetal blood transfusion was performed at 34 weeks 0 days as scheduled, via the umbilical vein at its placental insertion without complications, and the scheduled cesarean section was finally performed at 34 weeks 6 days, due to pain in the area of the previous operative scar and evidence of thinning of the uterine segment by ultrasound, a finding that was corroborated in the operative act.

The newborn was female, weighing 2,580 grams, size 41 centimeters, Apgar 6 at one minute and 9 at 5 minutes, yellow amniotic fluid. Weak cry, poor respiratory effort and subcostal retraction were observed in the newborn. The newborn was ventilated with a bag and Venturi mask with FiO2 0.21, recovering respiratory effort. However, it was decided to use continuous positive airway pressure (CPAP), thus improving respiratory distress.

In the following hours, arterial and venous umbilical vessels were catheterized, and laboratory tests were requested, which showed bilirubin values that indicated the need for exchange transfusion.

The first exchange transfusion was performed at 7 hours of life. Twenty exchanges of 20 mL each were indicated for a total of 400 mL. The procedure was performed without complications and intensive phototherapy was prescribed afterwards.

Despite the procedure, bilirubin levels remained in the exchange transfusion range, so it was decided to perform a second procedure at 20 hours of life, which was done with reconstituted blood O (-), 19 replacements for a volume of approximately 388 mL, without complications. The

newborn continued on CPAP and intensive phototherapy. In the following controls, the bilirubin results still showed values for exchange transfusion, and it was decided to perform a third exchange transfusion at 30 hours of life, with a replacement of 340 mL.

During hospital stay, cardiological evaluation showed left ventricular hypertrophy with preserved biventricular function. Evaluation by nephrology showed non-oliguric acute renal failure, with renal ultrasound displaying nonspecific nephropathy with poor corticomedullary differentiation. The renal Doppler ultrasound showed alterations in the flows, suggesting the avoidance of drugs that could cause nephrotoxicity and continuous monitoring of renal function every 48 hours.

Neuropediatrics found clinical signs of encephalopathy due to acute hyperbilirubinemia that required follow-up and assessment of auditory compromise with brainstem evoked potentials and early intervention with physical therapy.

The evolution of the newborn girl after the third exchange transfusion was optimal. At 6 days of life the CPAP was withdrawn, and she was left with a binasal cannula with good tolerance, which was withdrawn the following day, leaving her with spontaneous breathing without requiring oxygen. Likewise, bilirubin levels were decreasing, which allowed the withdrawal of phototherapy. Regarding nutrition, total parenteral nutrition was started at 5 days of life, after 4 days of fasting, and at 6 days of life oral tolerance was performed with good response. At 8 days of life, direct breastfeeding was started in addition to parenteral nutrition, with good response. At 9 days of life, parenteral nutrition was suspended, and the infant was exclusively breastfed. Difficulty in sucking was observed in the following days, so physical medicine and rehabilitation started sucking therapy. At 13 days of life, she was transferred from the incubator to the crib and skin-to-skin contact was initiated. An improvement in oral feeding was also observed with the help of physical therapy. Finally, it was decided to discharge her 25 days after birth, in good condition.

At her last check-up, at 18 months of age, the child's evaluations have been optimal, and her health condition is satisfactory.

Discussion

This is the first successful case of fetal intracardiac transfusion for severe anemia due to Rh isoimmunization published in our country. The severe fetal clinical picture led to perform this first emergency intracardiac transfusion, due to severe bradycardia and the difficulty in accessing the umbilical vein via the transplacental route due to placentomegaly secondary to fetal anemia.

Subsequent transfusions required were performed via transplacental access to the umbilical vein due to progressive clinical improvement of the fetus.

Intrauterine transfusion approaches are usually via the umbilical vein at the level of the placental insertion of the cord, in a free loop of the cord or at the level of the intrahepatic portion. However, the fetal intracardiac approach is also described, which has the advantage of being a larger target than venous access at the level of the cord or intrahepatic, but with the risk of producing bleeding and secondary cardiac tamponade.

The aim of the transfusion is to replace the fetal blood with Rh-negative donor blood, thus suppressing fetal erythropoiesis, also allowing to improve the fetal hemodynamic status to continue the pregnancy until the fetus is viable (ideally 36 weeks) and prevent fetal death. In the present case, in addition to improving fetal survival and prognosis, it greatly helped neonatal support. For transfusion it is important to keep in mind to use fresh red blood cells, screened to be virus-free, leukoreduced, irradiated, type O, Rh D-negative, crossmatched with a maternal sample and packed with a hematocrit of 75%-80%. Washed autologous maternal blood can also be used, which eliminates the risk of sensitization to new red cell antigens in random donor blood[13,14].

Intracardiac access for intrauterine transfusion or fetal blood sampling does not show success rates in published case series, but a complication rate of 5.6% to 6.5%. The complications reported in this type of procedure are similar to those described above, in addition to hemopericardium, damage to the atrioventricular valves, atrial damage, damage to the great vessels, damage to the conduction system and there may even be pulmonary trauma[15].

The recommended technique to perform an intracardiac transfusion requires, as for all intrauterine procedures, adequate counseling to the patient's mother so that she can understand the benefits of having a larger and more direct access to the cardiovascular system compared to the umbilical venous access; and also the risks related to the procedure and probable cardiac trauma. Therefore, it is proposed to give the parents options of other alternative procedures and even the possibility of choosing not to intervene by means of informed consent[16].

Entry through the right ventricle is recommended as it is the shortest route and reduces damage to the ventricular conduction system. Care should be taken not to damage the atrioventricular valves, the great vessels, and other structures such as lung and liver. The needle to be used should be long and thin, 21, 22 or 24 gauge, both for easy access to the fetal thorax and to limit the size of the puncture. After inserting the needle into the amniotic fluid, enter with the needle perpendicular to the chest wall to reduce the possibility of the fetal body rolling during the initial puncture and then place the needle into the right ventricle. After confirming that the tip of the needle is within the right ventricle, care should be taken not to penetrate the interventricular septum or damage the atrioventricular valves. Transfusion should be performed through a closed system to avoid gas embolism through the ductus arteriosus into the fetal systemic circulation. Before removing the needle, the fetal heart rate should be monitored and the pericardial space observed, and if there are no complications, the needle should be carefully removed. Post-procedure electronic fetal heart rate monitoring is suggested to exclude evidence of a non-reassuring fetal condition or the onset of uterine activity and follow-up ultrasound evaluation within 24 hours after the procedure[15].

Mackie et al[17]. reported a series of 8 fetuses who underwent fetal intracardiac transfusion, out of a total of 105 pregnant women who received intrauterine transfusion in 10 years. Gestational ages ranged from 17 to 21 weeks, most of the pregnant women (6 of 8) had a BMI >= 35 kg/m2 and all fetuses were hydropic. Two fetuses had anti-D isoimmunization and one had anti-Kell isoimmunization. The remaining 5 fetuses had severe anemia due to *Parvovirus* B-19. Two fetuses infected with *Parvovirus* B19 died of anemia and severe thrombocytopenia in addition to severe myocardial involvement. Complications during the procedure included severe bradycardia and asystole, inadvertent placement of the needle in the mitral valve and hemopericardium.

Complications observed by this procedure can sometimes be managed. Westgren et al[12], reported successful intrauterine resuscitation of 2 fetuses with intraoperative bradycardia by direct intracardiac instillation of epinephrine and also reported a successful pericardiocentesis after inadvertent entry into the right atrium, which apparently resulted in hemorrhage into the pericardial space.

A global study found that there is a gap of more than 80% of annual doses of anti-Rh(D) Ig not administered to patients who required it in several Latin American countries such as ours[18].

It is also noteworthy that this patient with previously applied immunoprophylaxis had problems of neonatal hemolytic anemia in the second pregnancy and early fetal hydrops. It is reported that in 1.8% of Rh-negative women without clinical evidence of isoimmunization receiving immunoprophylaxis with postpartum anti-D vaccine, the prophylaxis does not work, a problem that may have existed in this patient[19].

Conclusions

This case presented has allowed us to have the experience of performing an intracardiac blood transfusion in a fetus severely complicated by Rh isoimmunization and to report it as a valid resource for an additional access route in severe cases that require it.

The fetal and neonatal evolution guides us in the management of complicated fetuses with severe anemia. In addition, we keep learning that the earlier we detect the problem, the better the fetal and neonatal prognosis, without forgetting that immunoprophylaxis is the main weapon.

Referencias bibliográficas

1. Diamond LE, Blackfan K, Baty JM. Erythroblastosis fetalis and its association with universal edema of the fetus, icterus gravis neonatorium and anemia of the newborn. J Pediatr. 1932;1:269-309.
2. Levine P, Katzin EM, Burham L. Isoinmunization in pregnancy: its possible bearing on etiology of erythroblastosis foetalis. JAMA. 1941;116:825-27.
3. Moise KJ. Fetal anemia due to non-Rhesus D red cell alloinmunization. Semin Fetal Neonatal Med. 2008;13:207-14. doi: 10.1016/j.siny.2008.02.007
4. Moise KJ Jr, Deter RL, Kirshon B, Adam K, Patton DE, Carpenter RJ Jr. Intravenous pancuronium bromide for fetal neuromuscular blockade during intrauterine transfusion for red-cell alloinmunization . Obstet Gynecol. 1989;74:905-08. PMID: 2586956
5. Bevis DC. Blood pigments in haemolytic disease of the newborn. J Obstet Gynaecol Br Emp. 1956;63:68-75. doi: 10.1111/j.1471-0528.1956.tb05435.x
6. Liley AW. Liquor amnil analysis in the management of the pregnancy complicated by resus sensitization. Am J Obstet Gynecol. 1961;82:1359-70. doi: 10.1016/s0002-9378(16)36265-2
7. Liley AW. Intrauterine transfusion of foetus in haemolytic disease. Brit Med J. 1963;2:1107-9. doi: 10.1136/bmj.2.5365.1107
8. Rodeck CH, Kemp JR, Holman CA, Whitmore DN, Karnicki J, Austin MA. Direct intravascular fetal blood transfusion by fetoscopy in severe Rhesus isoinmunisation. Lancet. 1981;1:625-7. doi: 10.1016/s0140-6736(81)91549-x
9. Bang J, Bock JE, Trolle D. Ultrasound-guided fetal intravenous transfusion for severe rhesus haemolytic disease. Brit Med J. 1982;284:373-4. doi: 10.1136/bmj.284.6313.373
10. Nicolini U, Santolaya J, Ojo OE. The fetal intrahepatic umbilical vein as an alternative to cord needling for prenatal diagnosis and therapy. Prenatal Diagn. 1988;8:665-71. doi: 10.1002/pd.1970080906
11. Linderburg IT, van Kamp IL, van Zwet EW, Middeldorp JM, Klumper FJ, Oepkes D. Increased perinatal loss after intrauterine transfusion for alloinmune anaemia before 20 weeks of gestation. BJOG. 2013;120:847-52. doi: 10.1111/1471-0528.12063
12. Westgren M, Selbing A, Syangenberg M. Fetal intracardiac transfusion in patients with severe rhesus isoinmunization. BMJ. 1988;296:885-6. doi: 10.1136/bmj.296.6626.885
13. Moise KJ. Red blood cell alloinmunization in pregnancy. Semin Hematol. 2005;42:169-78. doi: 10.1053/j.seminhematol.2005.04.007
14. Huertas E. Anemia fetal, diagnostico y manejo actual. Rev Peru Ginecol Obstet. 2019;65:511-7. http://dx.doi.org/10.31403/rpgo.v65i2211
15. Sarno AP Jr, Wilson RD. Fetal cardiocentesis: a review of indications, risks, applications and technique. Fetal Diagn Ther. 2008;23(3):237-44. doi: 10.1159/000116748
16. Chervanak FA, McCullough LB. Ethical issues in recommending and offering fetal therapy. West J Med. 1993;159:369-99. PMID: 11643180
17. Fiona L. Mackie, Samantha J. Pretlove, William L. Martin, Veronica Donovan, Mark D. Kilby. Fetal intracardiac transfusion in hydropic fetuses with severe anemia. Fetal Diagn Ther. 2015;38:61-4. doi: 10.1159/000369798
18. Pegoraro V, Urbinati D, Visser GHA, Di Renzo GC, Zipursky A, Stotler BA, et al. Hemolytic disease of the fetus and newborn due to Rh(D) incompatibility: A preventable disease that still produces significant morbidity and mortality in children. PLoS ONE. 2020 July:15. doi: 10.1371/journal.pone.0235807
19. Bowman J. Rh-immunoglobulin: Rh prophylaxis. Best Pract Res Clin Haemat. 2006;19:27-34. doi: 10.1016/j.beha.2005.03.003