CLINICAL CASE

Nonimmune hydrops fetalis: case report

Hidropesía fetal no inmune. Informe de un caso

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Abstract

Background. Hydrops fetalis is a clinical condition characterized by an abnormal fluid accumulation in soft tissues and in some serous cavities of the fetus. It is important to determine beforehand if this condition is present in order to establish the most probable origin and to be prepared to administer optimal reanimation management of the neonate at birth. The care given to a newborn with hydrops fetalis is always a challenge for the neonatologist.

Case report. We present the case of a pregnant, nonisoimmunized patient with Rh O negative blood type. The following conditions were associated with her pregnancy: severe anemia, hypoalbuminemia, and preeclampsia/eclampsia. Delivery was accomplished with Cesarean section where a female neonate of 32 weeks gestation was delivered. Nonimmune hydrops fetalis was present.

Conclusions. We present recommendations for optimal diagnosis and therapy.

Key words: nonimmune, hydrops fetalis, preclampsia/eclampsia, hypoalbuminemia, anemia, prematurity

Resumen

Introducción: La hidropesía fetal es una condición clínica que se caracteriza por la acumulación anormal de líquidos en los tejidos blandos y en alguna de las cavidades serosas del feto. Es importante establecer con antelación esta condición, ya que debe conocerse la causa más probable, para ayudar en la mejor reanimación al nacimiento, la cual en el caso de un neonato con hidropesía fetal es un reto para el neonatólogo.

Presentación del caso: Se presenta el caso de una embarazada de grupo sanguíneo O Rh negativo, no isoinmunizada, que cursó con anemia y hipoalbuminemia graves, con eclampsia, de la cual mediante cesárea se obtiene un producto del sexo femenino, de 32 semanas de gestación, con hidropesía fetal no inmune.

Conclusiones: Se hace una revisión del tema con una discusión del abordaje diagnóstico y terapéutico actual.

Palabras clave: Hidropesía fetal no inmune, *hydrops fetalis*, preclampsia-eclampsia, hipoalbuminemia, anemia, prematurez.

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Hydrops fetalis is a clinical condition characterized by an abnormal accumulation of fluid that leads to an excessive extracellular accumulation in soft tissues (edema) and in some serous cavities of the fetus (pleural or pericardial effusion or ascites).[1-5]

Hydrops fetalis may be of immunologic (13% of cases) or nonimmunologic (87%) origin.[6] Under the first circumstance, the condition is usually secondary to maternal isoimmunization by Rh factor, and in the second it also includes cases with no evidence of circulating antibodies directed to erythrocyte antigens, i.e., they are considered to be of different origins.[7]

Care for the newborn with hydrops fetalis is a challenge for the neonatologist. When this condition is established with precedence, one should try to determine the most likely cause in order to better resuscitate at birth.[8] The objectives of this report are to present a case of nonimmune hydrops fetalis, a review of the topic, and to discuss the current management guidelines for these patients.

Clinical case

We present the case of a newborn whose 23-year-old mother had three pregnancies and two previous births. Date of the mother's last menstrual period was unknown. The mother's blood group was O Rh negative. Rhogam had been used in her previous pregnancies, which evolved without complications resulting in normal births and currently healthy children. Her current pregnancy was under control until the sixth month, at which time the pregnancy was complicated by severe anemia (7.1 g/dL) as well as severe hypoalbuminemia (2.3 g/dL). Two weeks prior, the patient presented with a urinary tract infection that was treated, and 10 days prior she had seizures associated with hypertension (cephalea, tinnitus, phosphenes). She was treated for eclampsia with anticonvulsant and antihypertensive. The anemia was not corrected before surgery because of the difficulty in obtaining concentrated O negative red cells. She received the full panel of treatment for fetal lung maturity.

The newborn was delivered on January 20, 2007 by Cesarean section with epidural block. The female infant weighed 2620 g, was 44 cm in length, and had a head circumference of 32 cm. Gestation was estimated at 32 weeks using the Capurro evaluation, with Apgar score of 2 (1 min), 4 (5 min) and 7 (10 min). She was revived with tracheal aspiration without result. Intermittent positive pressure bag and mask were also applied without adequate response so she was intubated with an endotracheal tube. The placenta was reported to be small and with amniotic fluid meconium+.

Initial physical examination showed marked tegumentary paleness, generalized edema, minor dysmorphias (hypertelorism, flattened nasal bridge, and short neck), well-ventilated thorax with moderate respiratory distress; hyperdynamic precordium and visible shock, soft systolic murmur; and globose, tense, prominent and brilliant abdomen with initial difficulty upon palpation of liver and spleen. Ascites was drained (4.5 and 3 cm from the costal margin). External genitalia showed edema++++, and extremities were Godet positive +++ with decreased muscle tone and strength. There was capillary refill in 2 to 3 sec (Figure 1).

Initial laboratory data showed the following: hemoglobin (Hb) 12 g/dL, hematocrit (Hct) 39%, leukocytes 10,200 mm^3, and platelets 237,000/mm^3. Blood group was O (Rh+). Total bilirubin was 5.7 mg/dL, indirect bilirubin was 5.4 and direct bilirubin was 0.3 mg/dL, Coombs' test was negative, total protein was 3.6 g/dL, and albumin 2.5 g/dL. Arterial blood gas had a pH of 7.21, $PaCO_2$ (30 mmHg), PaO_2 (41 mmHg), HCO_3 (15 mmol/L), base excess (-15.9 mmol/L), and oxygen saturation (63%).

Neonatal evolution

After endotracheal intubation during the first minutes of life, umbilical catheters were placed. The patient was fasted, metabolic acidosis was corrected and later management with amines was also added (dobutamine, 10 μg/kg/min and dopamine, 5 μg/kg/min).

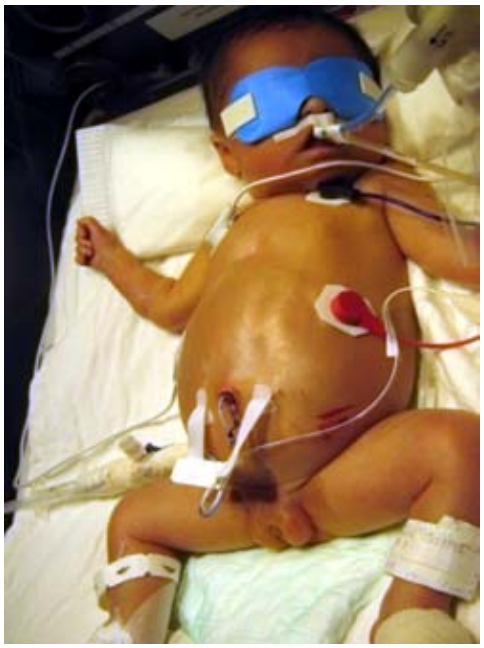

Figure 1. Phenotype shortly after birth.

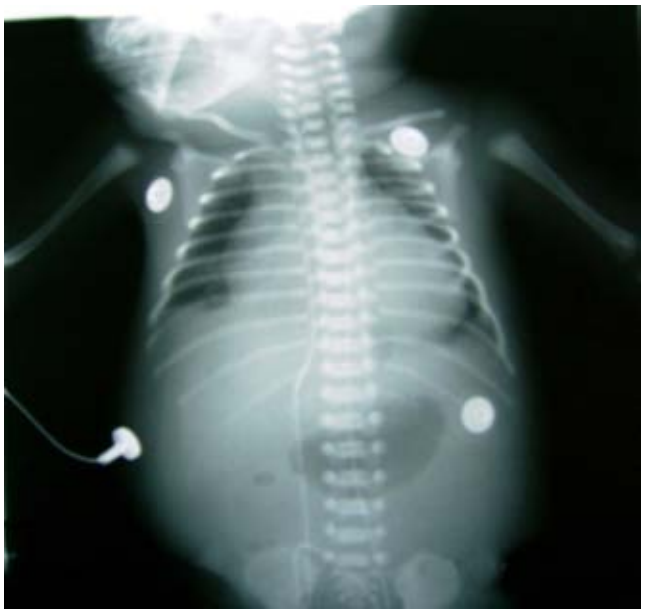

Figure 2. Initial chest x-ray with overall cardiomegaly without clear occupation of costophrenic and costodiaphragmatic angles. Abdomen with gastric bubble, remainder clear.

The patient evolved with ventilatory support. Right anterior pneumothorax was detected and managed conservatively. Chest x-ray showed severe cardiomegaly (Figure 2). Abdominal ultrasound (US) showed abundant ascites in which the abdominal viscera floated and pushed the intestines towards the mesogastrium (Figure 3). Transesophageal ultrasound (TUS) demonstrated peri-intraventricular hemorrhage (bilateral grade I) and periventricular echogenicity increased without peri-intraventricular or parenchymal calcifications.

The patient received two paracenteses with an interval of 18 h. A citrine-colored liquid was obtained (total 225 mL), which had a negative gram stain. The culture was reported without bacterial growth. Ampicillin/amikacin treatment was added because yellow, purulent discharge was reported with tracheal suction.

Electrocardiograms (ECGs) performed at 2, 5, 18 and 37 days of age ruled out structural cardiac alterations. Persistence was observed in patent ductus arteriosus with arterial pressure

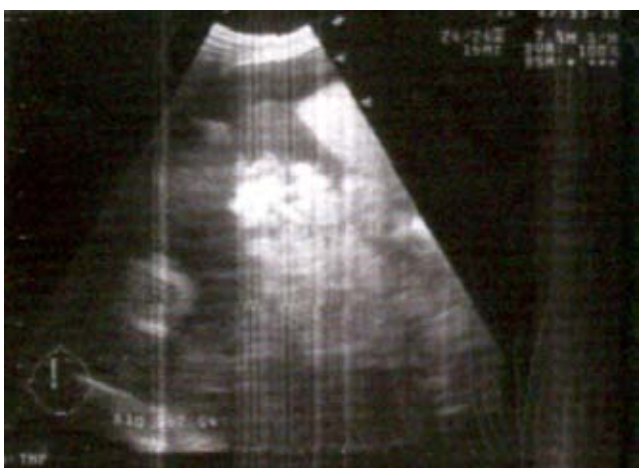

Figure 3. Abdominal ultrasound shows abundant ascites that moves abdominal viscera towards the mesogastrium.

(40 mmHg) (Figure 4). This was treated with fluid restriction, pulmonary vasodilator (captopril), cardiac tonic (digoxin) and diuretics (furosemide and later spironolactone); there was significant reduction in the cardiomegaly. Severe congestive heart failure was diagnosed, which gradually improved with the reported management.

Multifactorial jaundice, according to indirect bilirubin during the first days of life, was changed to direct beginning on the sixth day (4.21 mg/dL) and phototherapy was discontinued. Abdominal US was performed at 2, 3 and 18 days of age, the first to track ascites. In the last US, an alteration was discovered in the intra- and extrahepatic bile duct, mesentery, pancreas, and kidney. Only hepatosplenomegaly was observed, which has already been discussed.

After 5 days the patient presented respiratory improvement and hemodynamic stability and we electively extubated; however, on the eighth day we reintubated due to significant impairment in obstructive sleep apnea and cardiorespiratory arrest. There was good response to treatment and without impact to the common target organs, which allowed for extubation 48 h later. Antibiotic was changed due to the continuance of abundant yellowish-colored tracheal secretions. Subsequent TUS was reported with inconclusive US pattern of diffuse cerebral edema.

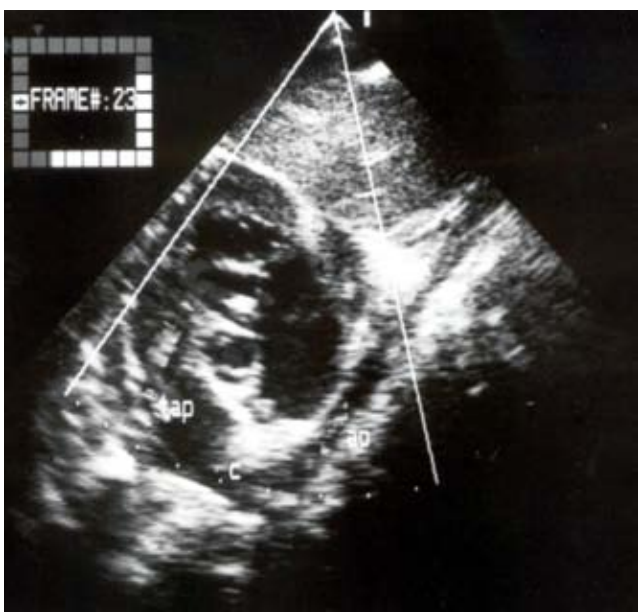

Figure 4. B-mode echocardiogram in subcostal short axis marking the level of large vessels where continuity between the pulmonary artery and descending aorta by the permeable arterial duct is observed.

Evolution beginning at 10 days after birth began with oral tolerance, decreasing the intake of protein and trace elements in parenteral nutrition that was suspended at 18 days after birth. At days 9 and 13, thrombosis of lower extremities was presented and a catheter was placed. Heparin treatment was initiated with good response in order for its withdrawal.

At 23 days of age, the patient was discharged from the neonatal intensive care unit (NICU) to continue her treatment in the nursery (Figure 5) where she continued to tolerate oral intake, allowing the gradual withdrawal of oxygen. Remitting direct hyperbilirubinemia was managed with ursodeoxycholic acid and was considered of multifactorial origin. After 24 days of life, the patient received a new treatment of antibiotics based on cefotaxime/vancomycin for suspected infection (yellowish-colored tracheal secretions, secondary atelectasis, gastric residue and intermittent oxygen desaturations of 74-78%). Treatment for chronic conductus arteriosus was suspended at 38 days. At 40 days of age, supplemental oxygen was suspended permanently and the patient then only received oxygen indirectly through the incubator. She was discharged to home within 45 days of life, with a corrected gestational age of 40 weeks and with normal neurological examination.

Figure 5. Phenotype at 23 days after birth (during the stay at the hospital nursery).

TORCH profile (including human immunodeficiency virus and VDRL) of the mother and the infant were reported as negative.

Fundus assessment by the Ophthalmology Department reported to the neonatologist no evidence of chorioretinitis, no cataracts and no retinopathy of prematurity.

Follow-up abdominal US showed no abnormalities in the liver, pancreas, intra- and extrahepatic biliary tracts, mesentery, intestine, and kidneys. ECG reported the persistence of conductus arteriosus in process of closing, with mild pulmonary hypertension (28 mmHg). Cranial US reported no malformations or periventricular or parenchymal calcifications. Amino acid chromatography was normal.

Discussion

This patient's condition was not able to be detected prenatally due to lack of prenatal care. When a prenatal US is performed, this problem can be detected beginning at 13 weeks of gestation and the etiology can be established in up to 50% of cases. If there are fetal heart rhythm disorders, use of maternal digoxin can reverse the hydrops.[9] Intrauterine transfusions can be used in the case of parvovirus B19 disease, fetal thoracic punctures or pleuro-amniotic derivations when the possibility of pulmonary hypoplasia is high. It is ideal to rule out severe chromosomal abnormalities and to establish the most appropriate delivery mode.

The first case of hydrops fetalis was reported in 1609 by a French midwife who reported the birth of twins. One of the twins was severely edematous and the other had severe jaundice. More than 100 years ago, Ballantyne established the clinicopathological criteria.[10] (Where are the references for the following 3 authors?) Potter (1943), Hoffman (1960) and Driscoll (1966) established US findings in the fetus: anasarca, serous effusion, edema of the umbilical cord and placenta accompanied by polyhydramnios. This remains as the best technique for prenatal diagnosis.

Birth conditions of the infant we are reporting on were critical and required neonatal resuscitation techniques. She received tracheal aspiration and positive pressure ventilation with bag and mask, as well as endotracheal intubation within minutes of life, according to the care guidelines that establish neonatal resuscitation in cases of meconium in the amniotic fluid and with a premature patient.[11] Apgar values were low (2/4/7). The literature indicates that 90% of these patients require tracheal intubation and 50% of patients had an Apgar score <6 at 5 min. Because of this, a team of specialists is necessary in the delivery room, capable of advanced neonatal resuscitation measures.[1,2]

If there is no improvement after intubation and assisted ventilation, an assessment must be made in the delivery room of the thoracentesis or abdominal paracentesis in the cases with pleural effusion or ascites. Placement of umbilical catheters aids in pH monitoring, blood gases, blood pressure and central venous pressure. It is necessary to measure hematocrit to assess urgency for blood transfusion.

It is important to stress the basic measures of neonatal resuscitation such as drying of a newborn and continuously measuring body temperature. It is essential to have adequate fluid replacement, electrolytes and glucose, often requiring blood products, albumin and diuretics. Due to not being widely recommended, these should be used cautiously.[12,13]

The patient suffered from mechanical respiratory restriction ascites, which was drained through two paracenteses in the first 24 h of life without complications, allowing much improved ventilatory support. The patient was treated with liquids based on ideal weight for gestational age as well as amines to improve congestive heart failure and the use of loop diuretics as conservative treatment for pericardial effusion. Upon improvement of the congestive heart failure, we used albumin for 24 h (total 2 g) mixed with an isotonic solution. There were no complications. Despite this treatment being controversial, it was used with the recommended precautions.[12-14]

One case of nonimmune hydrops fetalis is reported per 1500-7000 live births. The perinatal impact is reflected in high rates of mortality directly related to the cause and that have decreased from 50-90% in the 1970s to 40% in recent years in relation to the advancement of neonatal care.[3,5,6,14,15]

Maternal clinical history is fundamental because it will aid in the diagnosis: age, race, details of previous pregnancies, occupation, family history, etc. can all be related to specific pathologies.[7,16] As diagnostic methods improve, more causes come to light and, when no diagnosis is found, it is considered idiopathic.[14,17-21]

Table 1 describes the main causes associated with nonimmune hydrops fetalis. In this case, to determine the etiology once we ruled out maternal/fetal isoimmunization to Rh, we considered the most commonly reported causes: infections, congenital heart disease and chromosomopathy.[12-21] Our principal priority was to rule out congenital heart murmur and cardiomegaly, for which echocardiograms were performed on four different occasions without demonstrating structural heart disease. We found only closure in ductus arteriosus with pulmonary hypertension and the patient received treatment to support gradual and progressive closure based on the use of a cardiotonic diuretic as well as non-selective vasodilator for pulmonary hypertension. Complete closure was achieved at 37 days of life.

The patient appeared dysmorphic due to severe subcutaneous edema. The Genetics Service repeatedly assessed (with and without edema) the patient and found no signs of abnormal chromosomopathy, which is one of the major causes of this condition that can be detected in utero when there is opporutnity for prenatal US.[7] Amino acid chromatography was performed and we searched for a metabolic disease whose tracking should be considered in any patient with nonimmune hydrops fetalis. It is mandatory when there is a history of another child with hydrops. Result of amino acid chromatography was negative.[10]

Abdominal US ruled out intestinal malformations of the intra- and extrahepatic bile duct, liver, spleen, pancreas, kidney, and upper and lower urinary tracts. Determination of the binomial TORCH profile was negative and IgM and IgG were insignificant. VDRL was requested along with parvovirus B19, in addition to cytomegalovirus, toxoplasmosis, and herpes, all with negative results. TUS was reported without periventricular or parenchymal cal-

Table 1. Causes of hydrops fetalis

- **Severe chronic anemia in utero**
  Parvovirus B19-20%
  Homozygotic a-thalassemia
  Maternal/fetal transfusion or twin/twin
  Glucose-6 phosphate dehydrogenase deficiency
  Fetal Diamond-Blackfan anemia
  Congenital leukemia
- **Cardiac deficiency**
  Cardiomyopathy or severe myocarditis
  Premature closure of the foramen ovale
  Arteriovenous malformation
  Intrauterine arrhythmias
- **Hypoproteinemia**
- **Renal disease**
  Congenital nephrosis
  Renal vein thrombosis
- **Congenital hepatitis**
- **Intrauterine infection**
  Syphilis
  Toxoplasmosis
  Cytomegalovirus
  Parvovirus B19
- **Miscellaneous**
  Diabetes mellitus
  Multiple pregnancies
  Pregnancy-induced hypertension
  Umbilical or chorionic vein thrombosis
  Fetal neuroblastoma
  Cystic adenomatoid pulmonary malformation
  Pulmonary lymphangiectasis
  Chorioangioma of the placenta
  Transitory leukemia in patients with Down's syndrome
  Deficiency anemia
- **Chromosomopathies**
  Trisomies 13, 18, 21
  Monosomy XO
  Mosaicism

Source: References 9, 10, 13-20.

cification and there was no evidence of congenital brain malformation.

Gastroenterology Service assessed direct hyperbilirubinemia and reported this to be of multifactorial origin. The patient was fasted for 10 days and treated with parenteral nutrition for the first 18 days. Once the direct hyperbilirubinemia result was known, she was treated with ursodeoxycholic acid with gradual control of the process.

By exclusion, we consider that hydrops fetalis in this case was secondary to anemia, hypoalbuminemia and maternal hypertension during pregnancy. Hypoalbuminemia alone can cause hydrops fetalis, which is described by Islas-Domínguez and Jiménez-Jiménez[21] in two cases of non-immune hydrops fetalis. Serum albumin level of their patients was very similar to that of our case (1.9-2.4 vs. 2.3 g/dL, respectively).

The combination of these three maternal factors caused damage to a fetal microvasculature subjected to consistently high blood pressure with secondary endothelial damage, which is one of the three physiopathological mechanisms of accumulation and leakage of fluid into the interstitial spaces. In addition, this damage was enhanced by decreased colloid osmotic pressure in the plasma as well as the anemia and secondary cardiac insufficiency.[8,13,14]

This case is important to us because treatment response was favorable after cessation of the uterine microenvironment factors, stabilizing hemodynamic and respiratory conditions, and focusing on basic neonatal treatment. The diagnostic approach was used from the specific to the general, based on the clinical data. In our Department we have no report of surviving infants with nonimmune hydrops fetalis. Treatment of these patients is always a challenge because mortality has been reported in up to 90% of cases although it depends crucially on the cause of hydrops. This was essential for good outcome in this case because the patient did not present with severe congenital malformation.

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References

1. Rehan VK, Phibbs RH. Delivery room management. In: Mhairi G. MacDonald MG, Mullett MD, Seshia MMK, eds. Avery's Neonatology. Pathophysiology and Management of the Newborn. Philadelphia: Lippincott, Williams and Wilkins; 2005.
2. Blanchette V, Dror Y, Chan A. Hematology. In: Mhairi G. MacDonald MG, Mullett MD, Seshia MMK, eds. Avery's Neonatology. Pathophysiology and Management of the Newborn. Philadelphia: Lippincott, Williams and Wilkins; 2005.
3. Maya D, Leis MT, Hernández E, Karchmer SM. Hidropesía fetal no inmune: revisión de la literatura y presentación de una propuesta para su estudio y manejo. Perinatol Reprod Hum 1995;9:131-141.
4. Trainor B, Tumban R. The emerging pattern of hidrops fetalis?incidence, aetiology and management. Ulster Med J 2006;75:185-186.
5. Acho S, Díaz J, Guillen D, Bambarén E, Navarro R. Hidropesía fetal no inmunológica e infección intrauterina por citomegalovirus. Perinat Ginecol Obstet 2005;51:53-57.
6. De Haan T, Oepkes D, Beersma M, Walter F. Aetiology, diagnosis and treatment of hydrops fetalis. Curr Pediatr Rev 2005;1:63-72.
7. Cárdenas J, Huertas E, Oré I, Carvajal S. Hidrops fetalis no inmune: a propósito de un caso. An Facul Med 2004;65:133-137.
8. Núñez E, Varela S, Cervilla K, Shalper J. Hidrops fetalis causado por leucemia congénita. Rev Chil Pediatr 1991;62:186-188.
9. Greco P, Vimercati A, Giorgino F, Loverro G, Selvaggi L. Reversión de la hidropesía fetal y de la taquiarritmia fetal asociada con coma diabético materno. Eur J Obstet Gynecol Reprod Biol 2001;1:192-194.

10. Cheng I, Verp M, Knutel T, Hibbard JU. Mucopolysaccharidosis type VII as a cause of recurrent non-immune hydrops fetalis. J Perinat Med 2003;31:535-537.
11. American Heart Association and American Academy of Pediatrics. Textbook of Neonatal Resuscitation. Elk Grove Village, IL: American Academy of Pediatrics/American Heart Association; 2006.
12. Elias D, Ariello H, Izbizky G, Ferreira M, Lobos P, Fustiñana C, et al. Manejo interdisciplinario de un quilotórax congénito complicado con hidropesía fetal. Arch Argent Pediatr 2005;103:171-174.
13. Carlton DP, McGillivray BC, Schreiber M. Hidropesia fetal no inmunitaria: enfoque multidisciplinario. Clín Perinatol 1989;4:839-851.
14. López G, Ramírez AC, Fick E, Ibarra A. Hidropesía fetal no inmune. Presentación de siete casos. Rev Fac Med UNAM 2000;43:133-137.
15. Goh SL, Tan J, Kwek K, Yeo G. Recurrent non-immune fetal hydrops: a case report. Ann Acad Med 2006;35: 726-728.
16. García M, Cortez MA, Yeguez MFA, Pereira SD, Martínez OM, Valderrama CC. Hidrops fetalis: reporte de 8 casos. SALUS revista de la Facultad de Ciencias de la Salud. Universidad de Carabobo; 2004;8:3.
17. Santoloya J, Alley D, Islas-Domínguez LP, Verduzco-Gutiérrez M. Hidropesía fetal por hipoalbuminemia materna. Reporte de un caso. Rev Mex Pediatr 2003;70:291-294.
18. Xu J, Raff TC, Muallem NS, Neubert G. Hydrops fetalis secondary to parvovirus B19 infections. J Am Board Fam Pract 2003;16:63-68.
19. Dunbar AE, Moore SL, Hinson RM. Fetal Diamond-Blackfan anemia associated with hydrops fetalis. Am J Perinatol 2003;20:391-394.
20. Duque FA, Guerrero BS, Sotelo E, Martínez B, Brito J. Hidropesía fetal infecciosa: tratamiento en útero. Caso clínico. Rev Obstet Ginecol Venez 2000;60:119-125.
21. Islas-Dominguez LP, Jiménez-Jiménez JR. Dos casos de hidrops fetalis no inmune. Rev Mex Pediatr 2007;74: 216-221.