High Coombs Test Titers With No Fetal Anemia: Value of Middle Cerebral Artery Peak Systolic Velocity

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Received 29 October 2006; received in revised form 30 December 2006; accepted 31 December 2006; published online 20 February 2007

Abstract
Maternal Rh antibody titers increased progressively in a 26-years old black woman at her 4th pregnancy, but the stable and low middle cerebral artery peak systolic velocity (MCA PSV) suggested that the fetus did not develop anemia. Hemolysis did not occur. This case describes the ability of the MCA PSV in reflecting the not crossing-over of maternal antibodies to the fetus, even in the presence of high maternal anti-D antibodies titers.

Keywords: alloimmunization, fetal anemia, middle cerebral artery peak systolic velocity

Özet
Yüksek Coombs Test Titreleri Varlığında Orta Serebral Arter Maksimum Sistolik Akım Hızının Fetal Anemiği Belirlededeki Değeri


Anahtar sözcükler: alloimmunizasyon, fetal anemi, orta serebral arter maksimum sistolik akım hızı

Introduction
The fetus expresses Rh antigens on the red blood cells virtually as early in gestation as these are present. Once exposed, the mother mounts a competent antibody response against the fetal red blood cell antigens. With a first immune exposure to a given antigen, a primary immune response follows, in the form of the immunoglobulin M (IgM), which does not cross the placenta. The second exposure to that antigen results in the mature immune response. A sensitized woman is one with a detectable antibody. When this antibody is immunoglobulin G (IgG), it readily cross the placenta, as early as 10 weeks, and can cause fetal disease. As the antibody binds fetal red blood cells in circulation, it triggers fetal reticuloendothelial system digestion. With worsening anemia, the fetus compensates by maximising red blood cells production in the liver, spleen, intestinal wall and other sites to a minor extent, mediated by fetal erythropoietin. Amniotic fluid spectrophotometry (ΔOD450) correlates with the amount of bilirubin present. Since bilirubin is the endproduct of fetal disposal of the waste products of hemolysis, amniotic fluid bilirubin estimation gives information on the amount of hemolysis degree, and therefore on fetal anemia degree. Bilirubin can be quantitated most accurately by spectrophotometric measurements of the optical density between 420-460 nm, the wavelength absorbed by bilirubin. Amniocentesis with ΔOD450 evaluation provides ongoing reassurance that more invasive fetal testing is not yet necessary but rarely may provide false reassurance (1). Ultrasound examination represents an important tool on the evaluation of the alloimmunized fetus. Anemia does not appear to bear any pathognomonic fetal physical signs, and a serious degree of fetal anemia may be present without frank
hemoglobin and bilirubin after birth. The intrauterine life and with normal red blood cells counts, repeatedly with 1:8 until 20 week’s gestation. At 26 week’s gestation the indirect Coombs test was performed monthly at the Hematology Service and the anti-D antibody titer resulted to be 1:256 at 28 week, 1:512 at 29 weeks. The MCA PSV was 40-43 cm/sec at 30 weeks, 44-53 cm/sec at 31 weeks, 44-46 cm/sec in repeated evaluations at 32 weeks and 43-47 cm/sec at 33 weeks, thus, remaining always in the D risk zone. The patient was discharged and monitored as outpatient. Doppler velocity at 34 weeks and 4 days showed oligohydramnios. Despite the elevated anti D antibody titer was stable at 1:512, the MCA PSV was still 47 cm/sec. On the same day, five fetal heart rate traces were performed with evidence of low variability and late decelerations after low intensity uterine contractions. Cesarean section was performed the next morning, at 34 weeks and 5 days due to fetal heart rate alterations. A male of 2430 g and with a 8/9 Apgar score at 1st and 5th minutes was born. The newborn presented a blood ABO 0 and positive Rhesus and a direct Coombs test ++++ (titer 1:256). However, neonatologists did not report anemia findings at all (hemoglobin 17.5 g/dl, hematocrit 54.3%, erythroblasts 50% of the nucleated cells, bilirubin 3.4 mg/dl). The neonate was discharged one week after caesarean section and after continuous hematologic evaluations. A control evaluation after one month showed again good neonatal conditions and blood analysis confirmed no signs of neonatal anemia.

Case
The mother was a 26-years-old African woman from Ivory Coast at her 4th pregnancy. Obstetrical history included a spontaneous delivery in 1996 at 30 week’s gestation who died 9 hrs after birth for imprecise cause, a spontaneous abortion in 1999 at 8 weeks and a cesarean section at term in 2000 (blood group ABO and Rhesus positive, birthweight 2870 g) affected by anemia due to alloimmunization who underwent exchange transfusion and phototherapy. Only in last pregnancy anti Rh prophylaxis was administrated. At present pregnancy complete data regarding blood group of both fetus mother and father were obtained. Mother: group B, Rhesus negative, phenotype rhesus Ccdeee, Du negative, Kell Ag negative; Father: group 0, Rhesus positive, ccDee, K negative.

The indirect Coombs test was performed monthly at the Hematology Service and the anti-D antibody titer resulted repeatedly with 1:8 until 20 week’s gestation. At 26 week’s the titer increased to 1:128. It was decided to evaluate the MCA PSV. The measurements were performed by a single physician, with insonation angle <10° in both MCAs, and after a minimum of 15 minutes required for the analysis, the MCA PSV was related to a mean of five measurements (Figure 1). At 29 week’s gestation the patient was admitted to our Department. There was evidence of regular fetal growth (50°-75° percentile) and normal amniotic fluid volume; and MCA PSV was at 34 cm/sec. This value was compared with the MCA PSV curves (5) and corresponded to the D risk zone (low risk) for fetal anemia suggesting repeat evaluation after 2-3 weeks. It was repeated weekly because of increasing anti D antibody titer (1:128 at 26 weeks, 1:256 at 28 weeks, 1:512 at 29 weeks). The MCA PSV was 40-43 cm/sec at 30 weeks, 44-53 cm/sec at 31 weeks, 44-46 cm/sec in repeated evaluations at 32 weeks and 43-47 cm/sec at 33 weeks, thus, remaining always in the D risk zone. The patient was discharged and monitored as outpatient. Doppler velocity at 34 weeks and 4 days showed oligohydramnios. Despite the elevated anti D antibody titer was stable at 1:512, the MCA PSV was still 47 cm/sec. On the same day, five fetal heart rate traces were performed with evidence of low variability and late decelerations after low intensity uterine contractions. Cesarean section was performed the next morning, at 34 weeks and 5 days due to fetal heart rate alterations. A male of 2430 g and with a 8/9 Apgar score at 1st and 5th minutes was born. The newborn presented a blood ABO 0 and positive Rhesus and a direct Coombs test ++++ (titer 1:256). However, neonatologists did not report anemia findings at all (hemoglobin 17.5 g/dl, hematocrit 54.3%, erythroblasts 50% of the nucleated cells, bilirubin 3.4 mg/dl). The neonate was discharged one week after caesarean section and after continuous hematologic evaluations. A control evaluation after one month showed again good neonatal conditions and blood analysis confirmed no signs of neonatal anemia.

Discussion
In every Rh D negative pregnant woman, anti-D antibodies, if present, can be revealed by the indirect Coombs test. Because of factors such as the Rh antibody binding constant or avidity of the antibody for the antigen in the red blood cells membrane, and therefore its ability to produce hemolytic disease, the amount of Rh antigen in the red blood cell membrane and the ability of the fetus to maintain adequate circulating red blood cell hemoglobin varies. There exists a relatively poor correlation between blood group antibody titrations and severity of hemolytic disease. The antibody titer below which there is no risk for hydrops fetalis or stillbirth before term is conventionally 1:16. In the case presented here, an anti-D antibody titer at 1:128 prompted the decision to perform MCA PSV evaluation since it has the same effectiveness as ∆OD450 (6). The MCA PSV values measured weekly matched with the D low risk zone, indicating that the fetus was not anemic. All ultrasound examinations were normal. At third trimester evaluation, evidence of moderate oligohydramnios followed by fetal heart rate trace alterations were found. All ultrasound and fetal heart rate recordings were not related to maternal alloimmunization. Why the fetus did not develop anemia despite the high maternal anti-D antibody titer remains open. Possibly the maternal anti-D antibodies did not cross-over with fetal Rh antigens in the fetal circulation. Maternal Rh antibody titers increased progressively but
the stable and low MCA PSV suggested that the fetus did not develop anemia. Therefore, it was concluded that hemolysis did not occur. In fact, the newborn presented normal hemoglobin and bilirubin values. However, this is just a hypothesis that may just help us to explain and understand why the newborn did not develop anemia. Late decelerations of the heart rate are not related to hematological conditions since they appeared after uterine contractions in the environment of a non-reactive fetal heart trace monitoring.

This case describes the ability of the MCA PSV in reflecting the not crossing-over of maternal antibodies to the fetus, even in the presence of high maternal anti-D antibodies titers.

References