

Hemolytic disease of the
fetus and newborn – starting
with maternal anti-c antibo-
dies and ending with “bronze
baby syndrome”

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Sartorius G, Luecking-Famira KM, Schiesser M, Tercanli S, Holzgreve W, Fahnenstich H, University Women's Hospital (SG, SM, TS, HW), Neonatology Department, University Children's Hospital (LFKM, FH), Basel, Switzerland

A 27-year-old G1/P1 was referred to the obstetric ultrasound unit because of maternal anti-c antibodies, most probably due to a blood transfusion at the age of 14 because of Crohn's disease. Knowing the maternal (CCD. ee) and paternal (CcD. ee) rhesus phenotypes, the fetus was supposed to be heterozygous for c. The prenatal maternal anti-c antibody titer was 1:16 and rose continuously to 1:1000 at the 30 5/7 weeks of gestation. The middle cerebral artery (MCA) peak systolic velocity was below the 50th percentile. MCA peak systolic velocity climbed over the 95th percentile for the first time at 36 2/7 weeks of gestation (Fig. 1,2) after a further marked increase of the maternal antibody titer up to 1: 4000. Since fetal electronic monitoring revealed sinusoidal heart rate tracings (Fig.3) the infant was delivered by Cesarean section.

The infant was non-hydropic, pale and markedly jaundiced. Postnatal adaptation was otherwise prompt and undisturbed. The infants blood group was A Rh positive (CcD. ee) as expected, and the direct Coombs' test was strongly positive. Due to profound anemia (Hb 54 g/l) and a cord blood total bilirubin of 175 $\mu\text{mol/l}$ (conjugated bilirubin 11%, 19 $\mu\text{mol/l}$), an exchange transfusion was performed achieving stable hemoglobin values of 180 g/l. Despite immunoglobulin therapy and intensified phototherapy, total bilirubin values rose up to 500 $\mu\text{mol/l}$ with a markedly elevated conjugated bilirubin fraction up to 240 $\mu\text{mol/l}$. Hepatosplenomegaly and ascites were

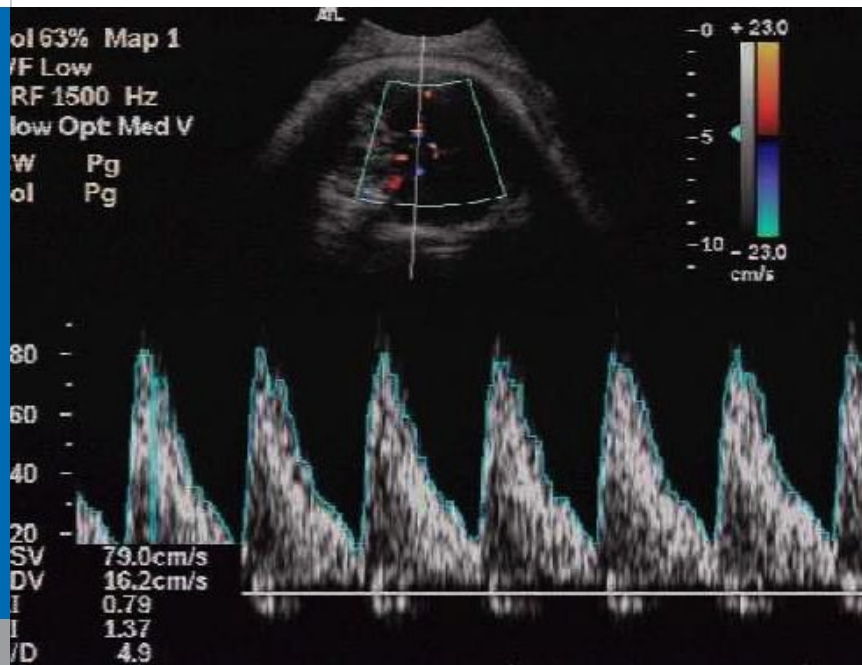


Fig. 1

MCA Doppler sonography.

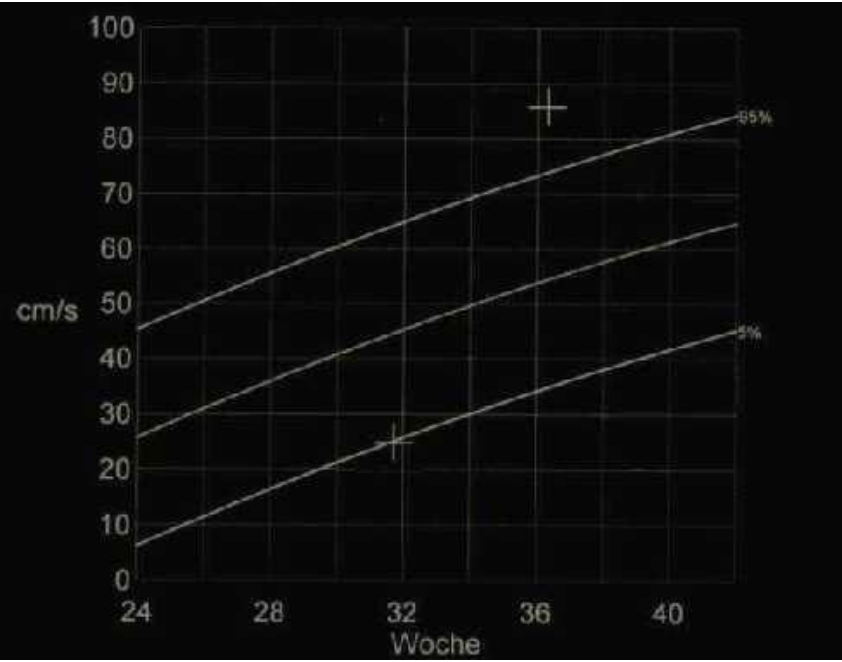


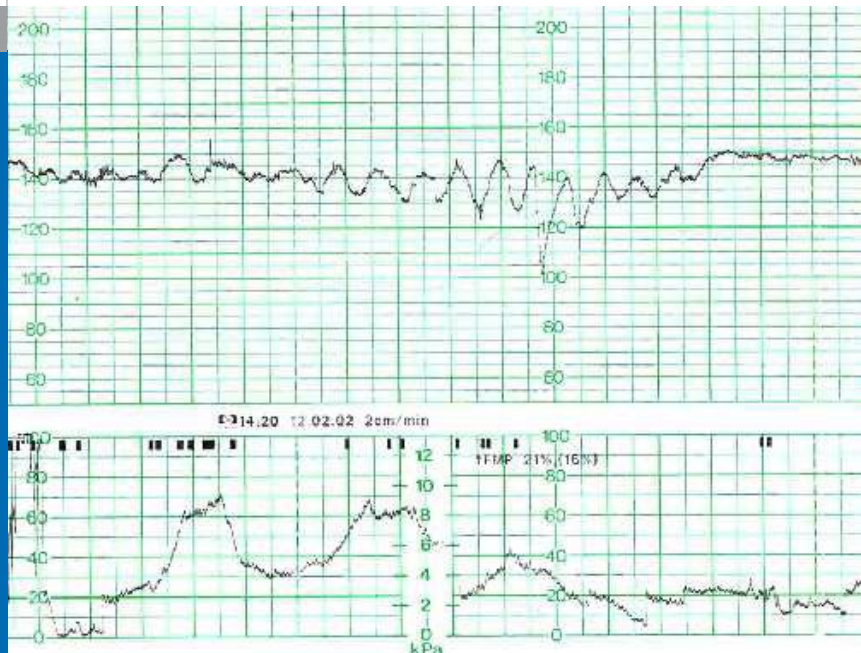
Fig. 2

Nomogram of MCA peak systolic velocity.

accompanied by pronounced reticulocytosis; liver enzymes were only mildly elevated. Ultrasonography revealed no sign of extrahepatic bile duct obstruction. Despite termination of phototherapy a “bronze baby syndrome” developed but gradually resolved.

Cardiotocogram (CTG).

Fig. 3



Hemolytic disease of the fetus and newborn (HDFN) is induced by transplacental transfer of maternal IgG antibodies against fetal erythrocyte membrane antigens. Despite prenatal immunoprophylaxis, most cases of red cell incompatibility still involve the classical rhesus D antigen. However, apart from rhesus D antigen more than 40 other red cell antigens have been implicated in HDFN, with c/C, e/E, Kell, Duffy and Kidd antigens being the most common (1).

Different from the hereditary mode of rhesus D/d, the phenotypes C/c and E/e are inherited in a co-dominant way. Therefore, fetuses who are heterozygous for one of those rhesus-antigens can suffer from severe hemolysis in utero when maternal antibodies enter the fetal circulation. Hemolysis can happen as early as in the 18th week of gestation. The production of many of the maternal antibodies could be avoided by the use of selected red blood cells when transfusing premenopausal women.

The most accurate method for diagnosing fetal anemia is direct measurement of the fetal hemoglobin concentration through cordocentesis. This procedure is associated with a complication rate of around 1%. The formerly common spectrophotometric examination of amniotic fluid („OD 450“) should no longer be used because it is invasive and not more helpful than the non-invasive method mentioned below (2).

Nowadays, the best non-invasive test to predict fetal anemia is the Doppler evaluation of the MCA peak systolic velocity (3) which is increased in anemic fetuses because of low blood viscosity. This method is recommended as the first-line monitoring tool in pregnancies at risk because it helps to determine the best timing for invasive procedures and therefore reduces the number of associated complications. When selecting a threshold value of 1.5 times the median of MCA peak systolic velocity the sensitivity for the prediction of fetal anemia even in fetuses without hydrops has been reported to be 100%, with a false positive rate of 12% (depending on gestational age) in a study of 111 fetuses at risk (4).

Neonatal cholestasis is a frequent complication in immune hemolytic diseases. Up to 16% of the affected children suffer from this complication. Even in utero, severely anemic (and therefore frequently transfused) fetuses can show elevated cord blood bilirubin values with an increased portion of conjugated bilirubin (5-7). The etiology is not known. One hypothesis is based on relatively insufficient transplacental clearing of fetal bilirubin, which leads to a stimulation of the glucuronyl-transferase-activity. A mechanically based hypothesis suggests that liver cell necrosis caused by profound anemia and subsequent hypoxemia plus additional compression of intrahepatic bile ducts by extramedullary hematopoiesis contribute to an insufficient active bile secretion. True inspissation of the bilious fluid has been suggested, but never proven.

Stimulated compensatory hematopoiesis in severe HDNF leads to an increased bystander production of porphyrins accumulating in various organ systems. Phototherapy can cause breakdown of various porphyrins sensitized by cutaneous bilirubin, thus leading to the green-grayish skin color seen in "bronze baby syndrome" (8). The prognosis for the child after termination of phototherapy is usually good.

Although anti-D remains the most common clinically important antibody in HDFN, anti-c and other antibodies are also associated with important fetal and neonatal morbidity, even in fetuses of heterozygous state. The best available non-invasive test for monitoring pregnancies at risk is the MCA peak systolic velocity measurement at one to two week intervals. With an MCA peak systolic velocity of 1.5 MoM or more, fetal anemia has to be suspected and should be confirmed or ruled out by cordocentesis.

CONCLUSION

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CONTACT Swiss Society of Neonatology
www.neonet.ch
webmaster@neonet.ch