# Anti-M Alloimmunization following Term Stillbirth: A Case Report and Review of the Literature

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## Abstract

Alloimmunization due to anti-M antibodies are rare since they present as naturally occurring immunoglobulin M antibodies, which do not cross the placenta. Very rarely, these may convert to immunoglobulin G antibodies and cause hemolytic disease of the fetus and newborn. We present the case of a fifth gravida, with previous two miscarriages and an unexplained stillbirth, booked with us for the 8 weeks. At booking, she was found to have anti-M antibodies with titers of 1:2, which was stable throughout pregnancy. At 35 weeks, there was evidence of severe fetal anemia and features of hydrops on the ultrasound scan, requiring delivery. Neonatal direct Coombs test was positive. Baby had a hemoglobin of 8.8 mg/dL and a reticulocyte count of 5.5% at birth, requiring two units of blood transfusion. He also required 6 days of intensive phototherapy. Alloimmunization due to anti-M antibodies should be suspected in women with previous bad obstetric history. The maternal antibody titers may not be a true reflection of the severity of fetal affection, and hence not reliable for monitoring in pregnancy

**Keywords**
- alloimmunization
- anti-M antibodies
- fetal hydrops
- hemolytic disease of fetus and newborn
- stillbirth

## Introduction

The most common cause of hemolytic disease of the fetus and new-born (HDFN), in the developing world, is alloimmunization due to anti-D antibodies. However, with widespread usage of postpartum anti-D prophylaxis, the prevalence of alloimmunization due to anti-D antibodies are showing a downward trend. The minor red cell antigens and their antibodies are emerging as important causes of alloimmunization.

More than 60 red cell antibodies have been identified in the etiology of HDFN.[1] Alloimmunization occurs in the presence of maternal immunoglobulin G (IgG) antibodies as immunoglobulin M (IgM) antibodies are too large to cross the placenta.

Nearly 21% of the Caucasian population and 26% of the African population lack the M antigen and produce antibodies when exposed to it.[2] Anti-M antibodies are naturally occurring IgM cold agglutinins. Their conversion to IgG antibodies is rare and can cause severe HDFN.[3] The prevalence of anti-M antibodies in the pregnant population ranges from 10 to 15%.[4]

We report the case of a pregnancy affected by anti-M alloimmunization, requiring delivery at 35 weeks. Neonate

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required intensive phototherapy (PT). A written, informed consent was obtained from the woman and her partner.

## Case Report

A 34-year-old multigravida, gravida 5, para 2, living 1, stillbirth 1, abortions 2 presented to us at 8 weeks gestation for antenatal care. She was married for 5 years; this was a nonconsanguineous union. Her risk factors included bad obstetric history and a previous lower segment cesarean section (LSCS). Her blood group was A positive. In her first pregnancy, she went into preterm labor at 36 weeks and underwent emergency LSCS for fetal distress. A girl baby weighing 1.48 kg and Apgar score (AS) of 8, 9 was born. The child is alive and well.

She subsequently had two missed miscarriages for which she was evaluated and her recurrent pregnancy loss (RPL) workup was negative. RPL workup included serum thyroid stimulating hormone, hemoglobin A1c (glycosylated hemoglobin), anticardiolipin antibody, beta-2 glycoprotein levels and lupus anticoagulant, and peripheral blood karyotyping for both partners to rule out balanced translocations. Indirect Coombs test (ICT) was not done at this time.

In her fourth pregnancy, the antenatal period was uneventful, with no history of gestational diabetes or hypertension. Mid-trimester anatomy scan was normal. At 37 weeks, she presented to the hospital with reduced fetal movements. Scan done confirmed intrauterine fetal demise with features of hydrops. She underwent emergency LSCS and delivered a macerated male stillborn weighing 3.1 kg.

During evaluation for stillbirth, ICT was found to be positive (4+) with presence of anti-Fyb, anti-JKB, anti-Leb, and anti-M antibodies. Anti-K antibodies were not present. Other causes of fetal hydrops were ruled out by doing Parvovirus B19 serology and Kleihauer Betke test. Genetic tests were not carried out since there were no structural anomalies in the baby. Placental biopsy did not show any abnormality.

In the current pregnancy, the dating scan confirmed the presence of a single live fetus. At booking, her ICT was positive 1:2 dilution with presence of anti-M antibodies. Other antibodies were not present in the current pregnancy

First-trimester combined screen was negative for aneuploidies. Morphology scan at 20 weeks was normal. Fetal echocardiography was done to rule out congenital cardiac anomalies at 24 weeks. In view of the past obstetric history, pregnancy was monitored closely, with 2 weekly visits in early pregnancy and weekly visits later. ICT titers were followed up serially and were stable at 1:2 throughout pregnancy

At 35 weeks, the patient came for a routine antenatal checkup. Scan done at that time showed amniotic fluid index of 21, with the presence of minimal fetal ascites and fetal hydrocele. Middle cerebral artery peak systolic velocity (MCA PSV) showed evidence of fetal anemia at 80 cm/sec, which was greater than 1.5 multiples of median for the gestational age.

On suspicion of early hydrops, she was immediately taken up for LSCS and delivered a baby boy weighing 2.5 kg with AS 9, 9 at 1 and 5 mins. Neonatal direct Coombs test was positive at birth.

At birth, the neonate was found to have pallor and hepatosplenomegaly. The Cord bilirubin levels were 5.01 mg/dL and the baby was started on double surface PT. At 6 hours of life, the baby was found to have a hemoglobin of 8.8 mg/dL and was given one unit of packed red cells. Neonatal reticulocyte count was 5.5%. The baby required PT for a total of 6 days.

On day 4 of life, baby had one episode of desaturation and the baby was started on continuous positive airway pressure support with positive end expiratory pressure of 5 cm of H2O. Severe acute respiratory syndrome coronavirus- 2 infection was ruled out and ammonia levels were normal. Capillary bilirubin was 18.4 mg % and the baby was restarted on double surface PT that a showed decreasing trend of bilirubin.

On day 5 of life baby had one episode of seizure that settled with levetiracetam. Lumbar puncture was carried out and cerebrospinal fluid obtained did not reveal any evidence of meningitis. Since C-reactive protein was negative, antibiotics were stopped after 72 hours. Bilirubin encephalopathy was thought of as a differential. Magnetic resonance imaging was advised but parents wanted to do this later. Baby was discharged on day 15 of life

After 20 days of discharge, the neonate was diagnosed to have anemia during routine follow-up and was given another unit of packed red cells. Mother's breast milk showed the presence of anti-M antibodies. Hence, breast feeding was stopped transiently in view of persistent anemia and presence of antibody in mother's milk. Following this, baby has been doing well.

## Discussion

The prevalence of HDFN due to anti-M antibodies in the Caucasian population is low. In a study done over 16 years, Stetson et al looked at 195 pregnant women with anti-M antibodies and found that none of the babies had severe HDFN, although nine babies required PT.[5]

This is, in contrast, to the findings by Li et al who found anti-M antibodies were the cause for HDFN in 55.5% cases (10/18) and were the second most commonly implicated antibodies in etiology of HDFN after anti-D antibodies in the Chinese population.[6] Nearly 60% cases of HDFN required intrauterine transfusion and there were two cases of intrauterine demise due to lack of timely intervention.[6] They reported that anti-M-related severe HDFN have been more commonly found in Asian population especially, Japanese[7] and Chinese.[8,9]

We report a case of alloimmunization due to anti-M antibodies. The woman had had two miscarriages followed by a term stillbirth. Red cell antibody screen done following the term stillbirth showed the presence of multiple anti-red cell antibodies. Hence, the reason for hydrops was thought to be secondary to fetal anemia secondary to severe red cell alloimmunization, which was not detected antenatally. However, in the current pregnancy, anti-M antibodies were detected at booking. The antibody titer was being monitored serially and was stable at 1:2 throughout pregnancy. At 35 weeks, she presented with fetal hydrops, diagnosed on ultrasonography.

 

A learning point from this case is that ICT needs to be a part of evaluation for term stillbirths, especially when associated with fetal hydrops, even if maternal blood group is positive.[10] This could lead to the detection of other red cell antibodies, such as anti-M, which have the potential to cause HDFN.

The dilemma in our case, however, was that critical titers for the anti-M antibodies are not known. This is unlike other red cell antibodies such as anti-D/C/E/c/e or anti-Kell where there are known standard critical titers (1:16 and 1:8 respectively) which, if reached, trigger the monitoring for fetal anemia and hydrops on serial scans.[11] Hence, we were falsely reassured by the stable low titers of anti-M antibodies, and fetal MCA PSV monitoring was not done.

Anti-M antibodies cause fetal anemia by two mechanisms: suppression of erythropoiesis and causing hemolysis. Fetuses and neonates with anti-M-associated HDFN had lower levels of reticulocytes on evaluation, suggesting incompatible erythropoiesis with severe hemolysis.[8,9] This maybe the reason why the maternal antibody titers cannot accurately predict severity of fetal affection.

Hence, one should be careful in interpreting ICT titers in cases of anti-M antibodies. Lower ICT titers have the potential to cause severe disease just like anti-Kell antibodies, especially among women of Asian ethnicity. Therefore, monitoring for fetal anemia with MCA PSV on scans is likely to be more reliable than antibody titers alone.

Financial Disclosure.
None.

Informed Consent
Taken.

Animal Research Statement
Not applicable.

Conflict of Interest
None.

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