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Transfusion Medicine | LETTER TO THE EDITOR

# Management of anti-Colton$^{a}$ alloimmunisation in pregnancy: a case report

Dear Sir,

Diagnosis and management of anti-Colton$^{a}$ (Co$^{a}$) alloimmunisation during pregnancy is a rare and challenging condition. Only five cases have been described up to now, four in the 1970s and one in 2008, but diagnosis and management have changed in the meantime (Smith *et al.*, 1970; Simpson, 1973; McIntyre *et al.*, 1976; Fuhrmann *et al.*, 1979; Michalewska *et al.*, 2008). We here present such a case, its management and favourable outcome.

Alloimmunisation of a Co$^{a}$-negative pregnant woman, carrying a Co$^{a}$-positive foetus, may cause haemolytic disease in the foetus and newborn (HDFN) (Smith *et al.*, 1970; McIntyre *et al.*, 1976; Michalewska *et al.*, 2008). Nowadays, monitoring is performed by laboratory testing of antibody titre, although it is unknown whether antibody titration is helpful (de Haas *et al.*, 2015). Of greater importance are doppler flow measurements of the peak systolic velocity of the middle cerebral artery (MCA-PSV) (Zimmerman *et al.*, 2002; Michalewska *et al.*, 2008; Moise & Argoti, 2012; de Haas *et al.*, 2015). In cases of foetal anaemia, intrauterine blood transfusion (IUT) by cordocentesis is established, challenged by the allocation of compatible blood (de Haas *et al.*, 2015).

A 32-year-old woman (blood group 0 RhD−-, RhC−, Rhc+, RhE−, Rhe+, K−, Co$^{a}$−) was admitted to our hospital at 20 + 3 gestational weeks (gw) with an alloimmunisation against blood group antigen Co$^{a}$ with increasing antibody titer. Antibody identification was performed by indirect antiglobulin testing (IAT) and enzyme (papain) testing using an in-house panel and Coombs and neutral cards (IAT/ID and papain/ID) (BioRad, Cressier, Switzerland) (Table 1). Titration was performed in IAT/ID using a Co$^{a}$-heterozygous test cell. A Co$^{a}$-antigen determination of the foetus' father, using IAT/ID and non-commercial anti-Co$^{a}$ and anti-Co$^{b}$ sera, showed that he was Co$^{a}$ homozygous. Monitoring of the foetus was performed every 1–2 weeks by MCA-PSV measurements (Table 2). Between 28 and 32 gw, the MCA-PSV gradually increased with values above the 95th percentile and a Monocyte Monolayer Assay (MMA) showed a value of 29% (Nance *et al.*, 1989), so that anaemia was suspected and foetal transfusion planned. We used Co$^{a}$-, RhD-, RhC-, RhE- and Kell-negative blood from a donor, as women between 0 and 50 years of age should be transfused with Rh/K phenotype compatible blood only, according to the Swiss recommendations. We did not use blood from the mother, as autologous blood donation during pregnancy is not a common procedure, but rarely performed procedure in Switzerland, especially in order to avoid lowering the mother's haemoglobin level. Besides, there is no possibility of freezing blood in Switzerland. At 32 + 4 gw a cordocentesis was performed. An immediate intrauterine transfusion was initiated already before the foetal blood result was present, in order to avoid a possible second cordocentesis due to a dislocated needle. Knowing the haemoglobin/haematocrit of the foetus and of the preserved blood for transfusion, one can calculate the amount of blood needed to reach an appropriate foetal haemoglobin/haematocrit, according to the reference values by Mari *et al.* (2000). As the intraoperative blood results showed a haemoglobin and haematocrit of 123 g L$^{-1}$ and 35·5%, respectively, transfusion was stopped. So far, 40 mL of RhD-, RhC-, RhE-, Kell- and Co$^{a}$ negative, irradiated and washed red blood cells, depleted for plasma and leucocytes, with a haematocrit of 81·3% were transfused, leading to a post-transfusion haemoglobin level and haematocrit of 168 g L$^{-1}$ and 48·7%, respectively. MCA-PSV decreased to normal values within minutes and remained stable (Table 2). Delivery was performed at 37 + 2 gw by elective caesarean as part of our standard protocol for alloimmunised pregnancies. Blood testing of the newborn confirmed blood group A RhD negative with antibodies against Co$^{a}$, detected by direct antiglobulin testing (DAT) (agglutination ++, eluate testing positive). Foetal umbilical cord haemoglobin and haematocrit levels were 156 g L$^{-1}$ and 47%, respectively (Table 1). Due to foetal hyperbilirubinaemia on the fifth day postpartum, the neonate was treated with phototherapy for 3 days (Table 1). This was the reason, why mother and child were discharged from hospital not before 8 days postpartum, both without complications.

Given the limited data on the relevance of antibody titer, close monitoring of the mother and foetus was justified. Repeated antibody screening was performed for early detection of a titre increase. Although a significant increase in antibody titre was documented, this did not reflect foetal anaemia. Unfortunately, a clear cutoff for anti-Co$^{a}$ antibody titres, leading to foetal anaemia, is lacking (de Haas *et al.*, 2015). In our and other cases of severe foetal anaemia, the antibody titre was measured at a level of 1 : 128 in IAT and in a case of mild HDFN the titer was only 1 : 32 (Simpson, 1973; McIntyre *et al.*, 1976; Michalewska *et al.*, 2008). Here, however, it is important to consider the different methods of antibody titre determination used in the 1970s and nowadays. Additionally, a MMA can be performed to evaluate the clinical significance of the antibody. Monocyte reactivity greater than 20% was initially reported to correlate with

Correspondence: Nina Kimmich, MD, Division of Obstetrics, University Hospital of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland. Tel.: +41-44-255 1111; Fax: +41-44-255 5107
e-mail: nina.kimmich@usz.ch

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**Table 1.** Haematological course of mother and foetus/neonate

| Gestational weeks | Anti-Co[a] titer | Maternal haemoglobin (g per L) | Maternal haematocrit (%) | Foetal/ neonatal haemoglobin (g per L) | Foetal/ neonatal haematocrit (%) | Neonatal blood bilirubin (mcmol $L^{-1}$) | Neonatal transcutaneous bilirubin (mcmol $L^{-1}$) |
|---|---|---|---|---|---|---|---|
| 6 + 3 | 2 | | | | | | |
| 10 + 2 | 8 | 121 | 36 | | | | |
| 13 + 2 | 16 | | | | | | |
| 16 + 3 | 32 | | | | | | |
| 20 + 3 | 128 | 129 | 37·6 | | | | |
| 30 + 3 | 16 | | | | | | |
| 32 + 4 (before transfusion) | | 127 | 37·5 | 123 | 35·5 | | |
| 32 + 4 (after transfusion) | | | | 168 | 48·7 | | |
| 37 + 1 | | 122 | 35·3 | | | | |
| 37 + 2 (caesarean) | | | | 156 | 47 | 39 | 59 |
| 1st day postpartum | | 117 | 35·8 | | 56 | 105 | 109 |
| 2nd day postpartum | | | | | 56 | 200 | 179 |
| 3rd day postpartum | | | | | | | 225 |
| 4th day postpartum | | | | | 55 | 276 | 241 |
| 5th day postpartum | | | | | 56 | 300 | |
| 6th day postpartum | | | | | 55 | 281 | |
| 7th day postpartum | | | | | 61 | 299 | |
| 8th day postpartum | | | | | 57 | 258 | |

**Table 2.** MCA-PSV values in the course of pregnancy

| Gestational weeks | MCA-PSV (cm $s^{-1}$) |
|---|---|
| 20 + 3 | 27 |
| 22 + 3 | 32 |
| 24 + 3 | 39 |
| 26 + 3 | 45 |
| 28 + 3 | 54[1] |
| 29 + 3 | 60[1] |
| 29 + 6 | 60[1] |
| 30 + 3 | 65[1] |
| 30 + 5 | 61[1] |
| 31 + 3 | 62[1] |
| 31 + 6 | 74[1] |
| 32 + 2 | 72[1] |
| 32 + 4 (before transfusion) | 72[1] |
| 32 + 4 (after transfusion) | 43 |
| 32 + 5 | 54 |
| 33 + 5 | 63 |
| 34 + 6 | 65 |
| 36 + 4 | 72 |

[1] Value above the 95th percentile of reference limits.

needs for transfusion (Nance *et al.*, 1987). Subsequent studies from the same author, however, indicated that the assay may not always predict the outcome of the infant, as seen in our case and should not be used to evaluate HDFN. Before diagnosing foetal anaemia by MCA-PSV, bilirubin extinction in amniotic fluid from amniocentesis was performed (Moise & Argoti, 2012; de Haas *et al.*, 2015). This method was used in the four cases in the 1970s, but required repeated amniocentesis with the risks of an invasive procedure (Simpson, 1973; McIntyre *et al.*, 1976; Fuhrmann *et al.*, 1979). Measurement of the MCA-PSV is the gold standard nowadays and was performed in our and Michalewska's case (Mari *et al.*, 1995; Michalewska *et al.*, 2008). Compared with that case, where MoM-values for the MCA-PSV cutoff were used, we used the reference values published by Kurmanavicius *et al.* (2001) (Mari *et al.*, 1995). However, in our case MCA-PSV values indicative for foetal anaemia also exceeded the MoM-values by Mari *et al.* (1995), (2000). No neonatal exchange or top-up transfusion was required in our case and in the ones of McIntyre *et al.* (1976) and Smith *et al.* (1970), but in the other cases (Table 3). Although MCA-PSV values were indicative for foetal anaemia in our case, blood values were almost normal for the age of gestation.

The neonatal hyperbilirubinaemia, treated with phototherapy for 3 days, was probably not due to alloimmunisation against Co[a], but in the context of intensified postpartum haemolysis.

A great challenge in anti-Co[a] alloimmunised patients is the allocation of compatible blood for transfusion. In Switzerland, this can be achieved by finding a donor through the 'DGTI Rare Donor Register' (http://www.iblutspende.ch/rare-donors.html), by autologous donation of maternal blood or by transfusion of washed maternal erythrocytes (not a common procedure, limited to rare cases with missing compatible blood donors). In this case, the possible selection was even smaller due to the 0 RhD negative blood group of the patient (only 6% of blood donors). Only seven donors were compatible for the constellation of RhD-, RhC-, RhE-, K- and Co[a]-negative donors in Switzerland and only three of them available at that time. Furthermore, preparation time of 2 – 3 days had to be taken into consideration.

**Table 3.** Course and outcome of the six cases

| Case | Anit-Co[a] titre | Amniocentesis (n) | Cord blood sampling (n) | Foetal anaemia | Intrauterine transfusion (n) | Neonatal anaemia | Neonatal transfusion (n) |
|---|---|---|---|---|---|---|---|
| Smith *et al.* (1970) | | 0 | 0 | None | 0 | None | 0 |
| Simpson, 1973 | 128 | 2 | 0 | Severe | 0 | Severe | 2 |
| McIntyre *et al.* (1976) | 32 | 1 | 0 | None | 0 | None | 0 |
| Fuhrmann *et al.* (1979) | | 2 | 0 | Mild | 0 | Severe[1] | 2[1] |
| Michalewska *et al.* (2008) | 128 | 0 | 3 | Severe | 1 | Severe | 5 |
| Our case | 128 | 0 | 1 | Mild | 1 | Mild | 0 |

[1]Due to bleeding out of a ruptured vessel in the presence of insertio velamentosa.

Unfortunately, non-invasive treatment options are not available up to date.

Anti-Co[a] alloimmunisation during pregnancy is a challenging situation. Both national and international blood donor registries are extremely helpful to identify compatible blood donors. Despite increased antibody concentrations, MCA-PSV and MMA, this case did not develop foetal or neonatal anaemia and did not require exchange transfusion after birth. Serologic methods can help to initiate foetal monitoring and doppler MCA-PSV measurements might be helpful to avoid serial amniocentesis or foetal blood samplings, but can also be misleading in some cases.

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## CONFLICT OF INTEREST

The authors have no competing interests.

N. Kimmich[1], B. Brand[2], H. Hustinx[3], A. Komarek[4] & R. Zimmermann[5] *[1]Division of Obstetrics, University Hospital of Zurich, Zurich, Switzerland, [2]Division of Haematology, University Hospital of Zurich, Zurich, Switzerland, [3]Division of Immunohaematology, Interregional Blood Transfusion SRC Ltd., Switzerland, [4]Division of Immunohaematology, Blood Transfusion Service SRK, Zurich, Switzerland, [5]Division of Obstetrics, University Hospital of Zurich, Zurich, Switzerland*

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