Case report

Massive foeto-maternal transfusion: how long are foetal blood cells detectable in the maternal circulation?

Fabrizio Signore[1], Laura Marchi[2], Nathalie Conti[3], Cinzia Orlandini[3], Annalisa Vidiri[4], Francesca Brugnolo[5], Franco Bambi[5], Simona Zaami[6], Giovanni Scambia[4], Anna F. Cavaliere[2]

[1]*Department of Obstetrics and Gynaecology, Santo Eugenio Hospital, ASL Roma 2, Italy;*
[2]*Department of Obstetrics and Gynaecology, Santo Stefano Hospital, AUSL Toscana Centro, Prato, Italy;*
[3]*Department of Obstetrics and Gynaecology, Misericordia Hospital, AUSL Toscana Sud Est, Prato, Italy;*
[4]*Department of Woman and Child Health, Fondazione Policlinico Universitario A. Gemelli IRCCS and Università Cattolica del Sacro Cuore, Rome, Italy;*
[5]*Blood Transfusion Service, Meyer Children's Hospital, Florence, Italy;*
[6]*Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, "Sapienza" University of Rome, Rome, Italy*

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Correspondence: Laura Marchi
e-mail: laura.marchi@uslcentro.toscana.it

INTRODUCTION

Massive foeto-maternal transfusion (FMT) is the passage into the maternal circulation of >20% of foetal blood volume. It is associated with high perinatal morbidity and mortality[1]. FMT affects approximately 0.3-1:1,000 births and in non-complicated near-term pregnancies is frequently idiopathic[1].Clinical manifestations are non-specific and are mostly represented by a decrease in active foetal movements (AFM). Foetal anaemia can be suggested by a sinusoidal rhythm on cardiotocography (CTG) and by high peak systolic velocity (PSV) of the middle cerebral artery (MCA); both tests, however, are liable to yield false negative results[1]. The conclusive diagnosis of FMT is based on maternal laboratory blood tests such as the Kleihauer-Betke, although the gold standard is currently flow cytometry which has been proven to be more sensitive and time-saving[2]. However, the latter test is not always available, and therefore FMT is to be considered when other possible origins of neonatal anaemia have been excluded. We aim to demonstrate the long-lasting persistence of foetal blood cells in the maternal circulation in a case of massive FMT. These data are useful in a clinical scenario when FMT is not immediately suspected or investigated.

CASE REPORT

A 29-year old G3P1, blood type A-positive, was admitted at 40 weeks of gestation due to decreased AFM. CTG monitoring (58 minutes) revealed normal baseline foetal heart-rate, reduced variability, deceleration and intermittent sinusoidal foetal heart (**Figure 1**), justifying an emergency caesarean section that resulted in the birth of a live male weighing 3,000 g, blood type O-positive. PSV of MCA was not performed because of the urgent need for surgical intervention.

Apgar scores reported at 1 and 5 minutes were 3 and 4, respectively, arterial blood gas test at birth showed pH 7.09, base excess –12.6, and haemoglobin (Hb) 3.5 g/dL. The newborn received red blood cell (RBC) transfusions but died 3 days after birth in the neonatal intensive care unit.

Neither placental abruption, nor alloimmunisation, nor any infective or genetic cause for anaemia were found.

In order to evaluate foetal blood cells in the maternal circulation, a flow cytometry test was performed nine days after delivery in a reference laboratory; analysis was not available at the hospital where the delivery took place and the delay in carrying out the test was due to organisational issues. Massive FMT equivalent to 146.8 mL blood loss was detected using

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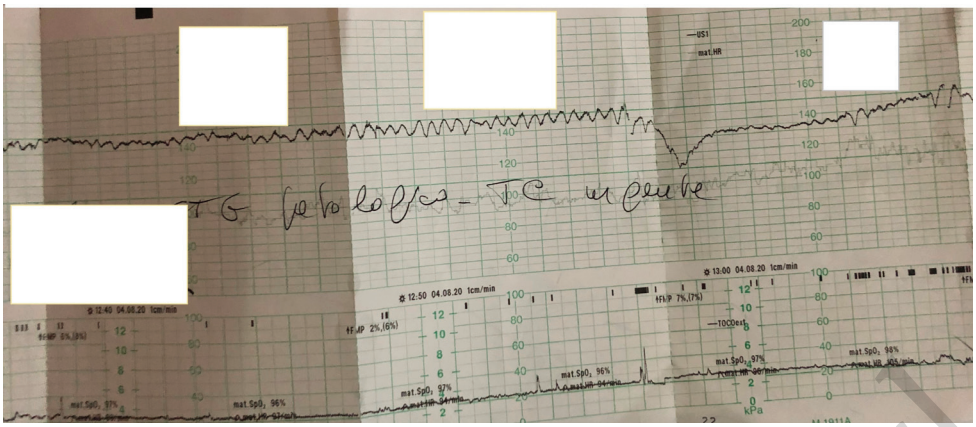

Figure 1 - Part of the intermittent sinusoidal cardiotocography

the Fetal Cell Count TM kit (IQ Products, Groningen, The Netherlands). This test was repeated 30 and 60 days later and 40 mL and 0.06 mL of foetal blood cells were detected, respectively; no foetal blood cells were detected at 90 days.

DISCUSSION

A small amount of foetal cells is found physiologically in the maternal circulation and constitutes the basis of non-invasive prenatal testing (NIPT)[3]. It has also been demonstrated that foetal cells can chronically persist in some maternal tissues: a phenomenon called microchimerism, which is held to be the cause of the increased incidence of some autoimmune diseases in women after delivery[4].

The massive passage of foetal blood cells, as reported in FMT, is associated with high perinatal morbidity and mortality (>10%) and is thought to be responsible for approximately 3-5% of unexplained foetal deaths[1].

In conditions causing foetal anaemia (e.g. foeto-maternal alloimmunisation or infectious disease including Parvovirus B19), active prenatal surveillance is undertaken to ascertain or identify in a timely fashion suspected low levels of Hb in the foetus.

There is no indication to investigate foetal anaemia in non-selected low-risk pregnancies, and FMT is often under-recognised because of slight or non-specific clinical signs such as maternal perception of reduced AFM. CTG, MCA-PSV and laboratory tests are useful tools to identify FMT.

A persistent sinusoidal foetal heart pattern on CTG is related to foetal anaemia; however, this may be a late sign of severe anaemia and only 52% of pregnancies were characterised by an abnormal intrapartum foetal heart rate tracing[5]. An intermittent sinusoidal pattern (as reported in our case) is rare and has been described in literature by Topping *et al*[6].

Doppler assessment of MCA-PSV is a good indicator of severe foetal anaemia, regardless of the aetiology, albeit its specificity gradually decreases at gestational ages >35 weeks[7]. The systematic review and case series of Bellussi *et al.* (2016)[8] concluded that MCA-PSV is the most effective predictor of severe FMT and all cases reported had MCA-PSV >1.5 MoM whereas an abnormal CTG was found in 66% of cases.

Flow cytometry is the gold standard to detect foetal Hb in the maternal circulation. This has replaced the Kleihauer-Betke stain test[9] the results of which can be compromised by many different factors such as temperature, pH, and the time of collection[10]. Both the Kleihauer-Betke test and flow cytometry, however, are burdened by false negative results in case of maternal-foetal ABO incompatibility, because maternal anti-A or anti-B isohaemagglutinins promptly destroy foetal RBCs[11]. In such cases, if FMT is strongly suspected, maternal haemolysis parameters and high α-foetoprotein may confirm the condition.

Evidence as to the lifespan of ABO-Rh-compatible foetal blood cells transfused into the maternal circulation remains inconclusive. Some studies report a shorter lifespan compared to adult RBC while others equate their lifespan with that of adult RBCs. Theses differences might

be related to the different age distribution of foetal cells and the time of FMT occurrence.

In our case, flow cytometry for FMT was performed 9 days after delivery. Foetal blood cells in the maternal circulation were detected 60 days after delivery but were undetectable 30 days later. This finding is in keeping with the literature. Indeed, collected data demonstrate a long-lasting persistence of foetal blood cells in the maternal circulation. Renaer[12] showed that ABO- and Rh-compatible foetal RBC disappeared 54 days after delivery. Harrison[13] found that foetal erythrocytes took up to 89 days to disappear. Rasmussen[14] detected foetal cells for 112 days after an FMT, while Dziegiel[15] reported that foetal cells were present up to 119 days after delivery.

FMT may have medico-legal consequence based on suspicion of negligence on the part of the obstetrician or untimely procedural practices. It is mandatory to take into account the fact that symptoms of an acute haemorrhage are non-specific and are, therefore, to some extent, misleading.

The forensic significance of a reasonably reliable assessment as to the timing of FMT is indisputable. In trials for malpractice, particularly when infants died or suffered major permanent damage, determining the timeframe of events could unveil negligence in terms of therapeutic interventions and treatment provision. Incorrect or absent diagnosis of the aetiology of foeto-neonatal anaemia has significant implications for our understanding of the epidemiology of FMT and could undermine efforts to provide thorough counselling for reproductive risk assessment to parents to prevent, as far as possible, such dramatic developments in future pregnancies.

CONCLUSIONS

There is no general consensus on an algorithm to apply in case of reduced AFM, and CTG and MCA PSV should be performed. In the case of unexplained foeto-neonatal anemia or death, FMT should be excluded as a possible cause. Flow cytometry is not a routine procedure, although it should be adopted given the possible medico-legal consequences. Our data demonstrate a long-lasting persistence of foetal blood cells in the maternal circulation, offering the opportunity to diagnose FMT at a later date.

Consent for publication was obtained from the patient.

AUTHORSHIP CONTRIBUTIONS

All Authors conceptualised and designed the study, drafted the manuscript, reviewed and revised the manuscript. All Authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Keywords: *foeto-maternal transfusion, flow cytometry, perinatal death.*

The Authors declare no conflicts of interest.

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