

Iron parenteral administration: an expert opinion on the assessment of fetal wellbeing

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Dear Sir,

Iron deficiency and iron deficiency anaemia represent global health issues¹. They lead to an increased risk of adverse outcomes (Table I) and appropriate management is essential². Among the new generation intravenous (IV) iron compounds, ferric carboxymaltose (FCM) is characterised by a free-dextrane structure which ensures less anaphylactic reactions; its nanomolecular stability minimises Fe³⁺ release³. As a result, FCM infusion is well-tolerated, facilitating rapid high-dose infusion. Data from two pharmacovigilance databases strengthen the evidence that iron isomaltoside 1000 is associated with a higher rate of severe hypersensitivity reactions than FCM³. In 2015, Woodward *et al.* reported the case of a woman who required an emergency caesarean section after IV iron isomaltoside 1,000 infusion⁴. Froessler *et al.* observed no adverse events in a cohort of pregnant women treated with FCM⁵. In July 2019, the European Medicines Agency (EMA) established that "fetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women". This recommendation has been made to the Italian Medicines Agency (AIFA) and added to the summary of product characteristics of all iron products. In pregnancy, iron administration is a life-saving therapy. Foetal heart rate (FHR) (normal range: 110-160 bpm) has been recognised as an important indicator of foetal wellbeing. In the past, it was assessed with a Pinard stethoscope. More recently, FHR has been evaluated in real-time using diagnostic ultrasound (US) imaging systems and Doppler auscultation or continuously by cardiotocography (CTG). As far as CTG is concerned, several randomised controlled trials have questioned its effectiveness in reducing perinatal morbidity and mortality because

Table I - Adverse maternal and perinatal outcomes in cases of iron deficiency anaemia

Adverse maternal outcomes	Adverse perinatal outcomes
Reduced physical activity	Preterm birth
Alterations of the cognitive performance status	Foetal growth restriction
Alterations of maternal immunological function	Intrauterine foetal death
Tiredness and increased depressive episodes	Low Apgar scores
Maternal death secondary to hypovolemic shock	Infant insufficient milk syndrome
Fluid overload and dilutional coagulopathy	Neonatal infection
Risk associated with surgical intervention	Neonatal intensive care unit admission

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of its limited specificity. In consideration of the EMA and AIFA recommendations, FHR in cases of pregnant women who need IV iron administration could be demonstrated by US, handheld Doppler US devices or foetal stethoscope, both at the beginning and at the end of iron infusion.

To conclude, according to real-life data, no cases of foetal bradycardia have been documented during FCM infusion since its commercialisation. To satisfy the summary of product characteristics of iron products, FHR will be evaluated both at the beginning and at the end of iron infusion using diagnostic US imaging systems, handheld Doppler US devices or foetal stethoscopes. The analysis of all available sources and the present Expert Opinion do not change the benefit/risk profile of FCM.

The use of IV iron is a central element of the application of the first pillar of Patient Blood Management and to improving clinical results. Therefore, the practical experience gained worldwide should be collected and made available in order to evaluate its safety in pregnant women.

The Authors declare no conflicts of interest.

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