A case of intracranial hemorrhage in a fetus with autoimmune hydrops after intrauterine transfusion

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Objective

To describe a case of fetal grade IV intraventricular hemorrhage due to IUT and review the literature about the fetal intracranial hemorrhage that occurred after intrauterine intravascular transfusion procedure in patients with Rh(D) alloimmunization.

Methods

We searched Pubmed, Scopus, EMBASE and Google Scholar databases using the keywords Rh isoimmunization 'OR' intrauterine transfusion 'AND' intracranial hemorrhage 'OR' brain injury 'OR' brain damage. We found only two paper that defines three cases of intracranial hemorrhage associated with intrauterine transfusion due to Rh alloimmunization.

Results

A 34-year-old woman gravida 3, para 2 with a history of an intrauterine death due to autoimmune hydrops, was referred to our center at 13 weeks' gestation. There were no pathologic findings in her physical examination, laboratory findings, and obstetric ultrasonography. She was followed up in the Prenatal Diagnosis and Treatment Unit by a protocol defined by the Society of Maternal-Fetal Medicine for alloimunized pregnant women. Her obstetric follow-up was unremarkable until 29 weeks of gestation. At 29 weeks of gestation, mid-cerebral artery peak systolic velocity (MCA-PSV) was detected 80.6 cm/s [>1.5 multiple of the median (MoM)] suggesting fetal anemia with ascites, cardiomegaly and pericardial effusion. An intrauterine intravascular transfusion was performed and the hemoglobin concentration before the procedure was detected as 2.9g/dL. 40 ml O Rh(D)negative red blood cell freshly prepared, underwent irradiation and leukodepletion were transfused to the fetus via the umblical vein in the portion of the umbilical cord near its insertion into the placenta by a 22-gauge needle with no complication. Post transfusion hemoglobin was detected as 8.1 g/dl. The initial and post transfusion platelet count were detected in the normal range (154000/ µl and 163000/ µl respectively). A few days later; ultrasound examination revealed the presence of an echogenic collection involving right lateral ventricle and extending to the surrounding cerebral parenchyma compatible with grade IV intraventricular hemorrhage. The couple was counseled and opted for the continuation of in utero therapy. The second IUT was scheduled after ten days. At 30+4 weeks of pregnancy, the second IUT was performed. The initial hemoglobin value was detected 4.9 g/dl. Persistent fetal bradycardia was noted during the procedure and an emergency cesarean section was performed. A APGAR score 4/7, 1315 g, 43 cm male infant was delivered by cesarean section. He was transferred to the neonatal intensive care unit. Exchange transfusion, phototherapy and intravenous immunoglobulin treatment were applied. Postnatal cranial ultrasonography showed diffuse echogenicity extending from the inferior left caudate nucleus to the left ventricle leading to it's dilatation which was compatible with intraventricular Grade IV hemorrhage. The intracranial hemorrhage had gradually regressed in the subsequent ultrasonographic examinations and completely disappeared at the end of the first month. The neonate was discharged from the hospital, healed, two months after delivery. At six months (time of writing of this paper), the baby shows normal neurological development. Fetal intracranial hemorrhage as a short-term neurological morbidity was reported by Ghi et al. for the first time in 2003. They described four cases with intracranial hemorrhage related to the fetal anemia (two immune hydrops due to Rh D alloimmunization, two monochorionic twin complicated with the death of the co-twin). Consistently with the case currently reported, each of the cases related with Rh alloimmunization had very low initial hemoglobin values in the first IUT (1.2g/dl and 1.6g/dl respectively). They suggested that disruption of intracranial vessels may be responsible in the pathophysiology of brain injury in severe anemic fetuses and stress the importance of fetal neurosonography in pregnancies with severe anemia due to Rh alloimmunization undergoing IUT. In 2004, the same group reported multiplanar neurosonography results of seven consecutive hydropic fetuses undergoing intrauterine transfusion procedure due to Rh alloimmunization. In addition to previously reported two cases, they described a case of periventricular leukomalacia and a case of unilateral ventriculomegaly that was noticed after the first IUT. In our case, the initial and post transfusion platelet values were detected in the normal range (154000/

µl and 163000/ µl respectively), and there was no sign of increased bleeding time such as excessive bleeding from the umblical cord after withdrawal of the needle. Furthermore, we hypothesized that preservative-anticoagulant system such as additive solution-1 (AS-1), AS-3, AS-5, citrate-phosphate-dextrose-adenine-1 (CPDA-1), citrate-phosphate-dextrose (CPD), citrate-phosphate-dextrose-dextrose (CP2D), that were used in red blood cell preparation, might predispose to intracranial hemorrhage by altering the coagulation system of the fetus. Thus, we proposed that removing these anticoagulants from the transfusion aliquots before intrauterine transfusion by centrifugation and volume reduction could be a beneficial measure to prevent hemorrhagic complications of this treatment. Simonazzi et al. demonstrated the risk of cerebellar damage in fetuses with severe anemia due to RhD alloimmunization after intrauterine intravascular transfusion procedure. They reported three cases of intracranial hemorrhage involving cerebellum, two of them previously reported by Ghi et al. In the third case, they performed first IUT at 22 weeks of gestation and after two weeks they noted suspicious cerebellar infarction in prenatal ultrasonography. In postnatal magnetic resonance imaging, bilateral cerebellar hemosiderin staining reported suggests prior hemorrhage. They emphasized that intracranial hemorrhage occurred at the infratentorial part of the brain particularly in intracerebellar hemispheres in all of the tree cases. Furthermore, in addition to hypoxia/ischemia, they also noticed the possible serious effect of sudden fluctuations in cerebral blood flow and arterial blood pressure (hyperdynamic circulation) on the intracranial hemorrhage. In our case, fetal anemia and hydrops were detected at the 28th week of gestation that was developed later compared with the other cases previously reported. Moreover, intracranial hemorrhage was identified in the right lateral ventricle and extending to the surrounding cerebral parenchyma compatible with grade IV intraventricular hemorrhage. Therefore, we considered that intracranial hemorrhage risk is not related to a gestational week of the first IUT in the presence of Rh(D) alloimmunization and post transfusion intracranial hemorrhage is not specific only the infratentorial region of the brain. Consistently with the cases reported previously, intracranial hemorrhage occurred after the first intrauterine intravascular transfusion.

Conclusion

In conclusion, in this study, a case of intracranial hemorrhage in a fetus with hydrops fetalis due to Rh alloimmunization after intrauterine intravascular transfusion has been presented and a comprehensive, up-to-date review has been performed. Although intracranial hemorrhage is a rare complication of IUT, clinicians should be aware of increased risk of brain damage in fetuses with Rh(D) alloimmunization undergoing this procedure. Detailed sonographic examination of the fetal central nervous system before and after the treatment should be performed in patients that are planning IUT. Also, communicating with blood bank to decrease the additive anticoagulant agents as minimal as possible in the preparation process of red blood cells and reduction of first transfusion volume to avoid sudden fluctuations in cerebral blood flow may be helpful to prevent this complication.

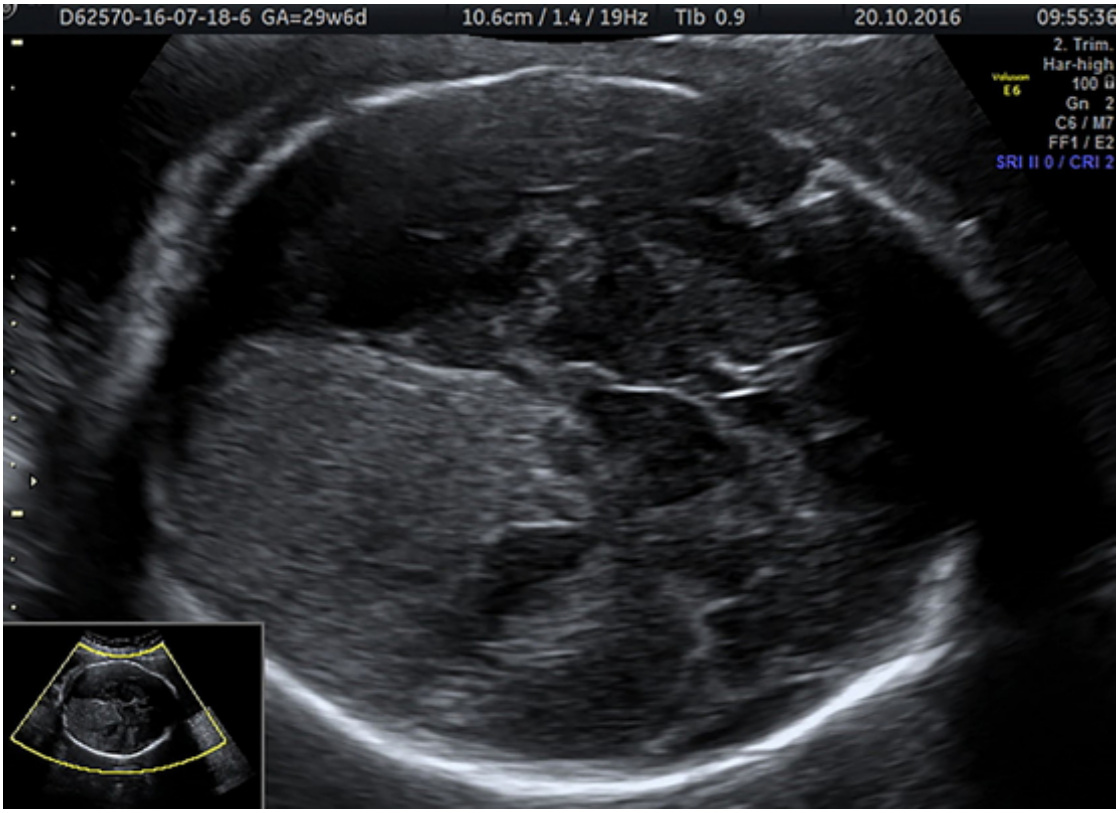

Table. Summary of reported fetal intracranial hemorrhage cases related with intrauterine transfusion due to Rh alloimmunization.

Authors	Case	Maternal age	Gestational age	Pretransfusion hemoglobin value (g/dl)	Pretransfusion platelet value (/µl)	Neurosonogram after the first intrauterine transfusion	Outcome
Ghi et al. 2004	Case 1	30	20	1.2	168000	Intraventricular and cerebellar hemorrhage	Termination of pregnancy. Pathological confirmation of cerebellar hemorrhage
	Case 2	25	23	1.6	177000	Cerebellar hemorrhage	Progressive hypoplasia of one cerebellar hemisphere. Delivery at 34 weeks after six IUTs. Normal neurological development at 2 years
Simonazzi et al. 2016	Case 3	32	22	4	-	suspicious cerebellar infarction	Hemosiderin staining in the cerebellum bilaterally, reflecting prior hemorrhage in postnatal brain MRI. Normal neurological development at 14 months.
Current study	Case 4	34	28	2.9	154000	an echogenic collection in the right lateral ventricle and extending to the surrounding cerebral parenchyma compatible with grade IV intraventricular hemorrhage	diffuse echogenicity extending from the inferior left caudate nucleus to the left ventricle that leads left ventricular dilatation (intraventricular Grade III hemorrhage). Normal neurological development at 6 months.