Case Report

Sonographic Demonstration of Intracranial Hemorrhage in a Fetus with Hydrops Fetalis due to Rh Alloimmunization after Intrauterine Intravascular Transfusion: A Case Report and Review of the Literature

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Intrauterine transfusion is the most common and successful intrauterine procedure for the treatment of fetal anemia due to red cell alloimmunization [1]. The beneficial effect of in utero therapy on perinatal survival has been demonstrated clearly in several observational studies [2, 3]. Despite the dramatic decrease in the IUT requirement due to the widespread use of prophylactic Rh(D) immune globulin, the procedure continues to be a gold standard for treatment of severe fetal anemia [4]. While intrauterine intravascular transfusion has remarkable effect on the treatment of fetal red blood cell alloimmunization, the total procedure-related complication rate has been reported approximately 3.1 percent and commonly indicated as fetal death, neonatal death, emergency cesarean delivery, infection, and premature rupture of membranes [5]. Fetal brain injury is a very rare complication of IUT that has been demonstrated only in a few case reports in the literature. Herein, we described a case of grade IV intraventricular hemorrhage that was diagnosed following the first intrauterine transfusion and reviewed the literature about the fetal intracranial hemorrhage that occurred after intrauterine intravascular transfusion procedure.

1. Introduction

Intrauterine transfusion (IUT) is the most common and successful intrauterine procedure for the treatment of fetal anemia due to red cell alloimmunization [1]. The beneficial effect of in utero therapy on perinatal survival has been demonstrated clearly in several observational studies [2, 3]. Despite the dramatic decrease in the IUT requirement due to the widespread use of prophylactic Rh(D) immune globulin, the procedure continues to be a gold standard for treatment of severe fetal anemia [4]. While intrauterine intravascular transfusion has remarkable effect on the treatment of fetal red blood cell alloimmunization, the total procedure-related complication rate has been reported approximately 3.1 percent and commonly indicated as fetal death, neonatal death, emergency cesarean delivery, infection, and premature rupture of membranes [5]. Fetal brain injury is a very rare complication of IUT that has been demonstrated only in a few case reports in the literature [6]. To the best of our knowledge, the literature does not include any cases of a grade IV intraventricular hemorrhage due to IUT.

Herein, we described a case of grade IV intraventricular hemorrhage that was diagnosed following the first IUT and reviewed the literature about the fetal intracranial hemorrhage that occurred after intrauterine intravascular transfusion procedure in patients with Rh(D) alloimmunization. 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 papers that define three cases of intracranial hemorrhage associated with intrauterine transfusion due to Rh alloimmunization. The initial platelet value was not noted in the third case. Author, case number, patient’s age, gestational age, pretransfusion hemoglobin value, pretransfusion platelet value, neurosonogram after the first intrauterine transfusion, and the outcome were summarized in Table 1. In this paper, we have compared our case with the other three cases we have found in the literature.

2. Case Presentation

A 34-year-old woman, gravida 3, para 2, with a history of an intrauterine death at 32 weeks of gestation due to hydrops fetalis as a result of Rh alloimmunization in the previous
<table>
<thead>
<tr>
<th>Authors</th>
<th>Case number</th>
<th>Maternal age</th>
<th>Gestational age</th>
<th>Pretransfusion hemoglobin value (g/dl)</th>
<th>Pretransfusion platelet value (/μl)</th>
<th>Neurosonogram after the first intrauterine transfusion</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghi et al. 2004</td>
<td>Case 1</td>
<td>30</td>
<td>20</td>
<td>1.2</td>
<td>168000</td>
<td>Intraventricular and cerebellar hemorrhage</td>
<td>Termination of pregnancy. Pathological confirmation of cerebellar hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>25</td>
<td>23</td>
<td>1.6</td>
<td>177000</td>
<td>Cerebellar hemorrhage</td>
<td>Progressive hypoplasia of one cerebellar hemisphere. Delivery at 34 weeks after six IUTs. Normal neurological development at 2 years</td>
</tr>
<tr>
<td>Simonazzi et al. 2016</td>
<td>Case 3</td>
<td>32</td>
<td>22</td>
<td>4</td>
<td>-</td>
<td>Suspicious cerebellar infarction</td>
<td>Hemosiderin staining in the cerebellum bilaterally, reflecting prior hemorrhage in postnatal brain MRI. Normal neurological development at 14 months</td>
</tr>
<tr>
<td>Current study</td>
<td>Case 4</td>
<td>34</td>
<td>28</td>
<td>2.9</td>
<td>154000</td>
<td>Echogenic collection in the right lateral ventricle and extending to the surrounding cerebral parenchyma compatible with grade IV intraventricular hemorrhage</td>
<td>Diffuse echogenicity extending from the inferior left caudate nucleus to the left ventricle that leads left ventricular dilatation (intraventricular grade IV hemorrhage). Normal neurological development at 6 months</td>
</tr>
</tbody>
</table>
The inferior left caudate nucleus to the left ventricle that ultrasonography showed diffuse echogenicity extending from this region. Neonate was transferred to the neonatal intensive care unit 4/7, 1315 g, 43 cm male infant was delivered by cesarean section. APGAR score was 4/7, and the initial hemoglobin value was detected as 4.9 g/dl. Persistent anemia before 20 weeks of gestation, and occurrence of fetal hydrops [9]. The presence of fetal hydrops during the first IUT reduces the success of the treatment. Lindenburg et al. reported the perinatal outcome of 491 fetuses who underwent 1422 intrauterine intravascular transfusion procedure during the antenatal period. They demonstrated that perinatal survival rate was 83% and 95% in hydropic and non-hydropic fetuses, respectively [10]. Although IUT contributes to the reduction of perinatal mortality, concerns about the neurological morbidities associated with this procedure have been considered only in a few studies [11]. Fetal intracranial hemorrhage as a short-term neurological morbidity was reported by Ghi et al. for the first time in 2003 [12]. They described four cases with intracranial hemorrhage related to the fetal anemia (two immune hydrops due to Rh D alloimmunization, two monochorionic twins complicated with the death of the cotwin). Consistently with the case currently reported, each of the cases related to Rh alloimmunization had very low initial hemoglobin values in the first IUT (1.2 g/dl and 1.6 g/dl, resp.). They suggested that disruption of intracranial vessels may be responsible in the pathophysiology of brain injury in severe anemic fetuses and noticed 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 [13]. In addition to the previously reported two cases, they described a case of periventricular leukomalacia and a case of unilateral ventriculomegaly that was noticed after the first IUT. They speculated that hypoxia/ischemia and the hyperdynamic circulation in fetal anemia cause the brain vessel disruption that leads to intracranial hemorrhage. They also considered that altered coagulation due to IUT might be responsible for intracranial hemorrhage. In our case, the initial and posttransfusion platelet count was detected in normal range (154000/μl and 163000/μl, resp.). A few days later, ultrasound examination revealed the presence of an echogenic collection involving right lateral ventricle and extending to the surrounding parenchyma compatible with grade IV intraventricular hemorrhage (Figure 1). The couple was counseled, and they 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 as 4.9 g/dl. Persistent fetal bradycardia was noted during the procedure, and an emergency cesarean section was performed. APGAR score 4/7, 1315 g, 43 cm male infant was delivered by cesarean section. Neonate 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 that leads to left ventricular dilatation compatible with intraventricular grade IV hemorrhage. The intracranial hemorrhage was gradually regressed in the subsequent ultrasonographic examinations and completely disappeared at the end of the first month, and the neonate was discharged from the hospital after healing two months after birth. At the time of writing this paper, the baby was showing normal neurological development at 6 months.

3. Discussion

Intrauterine transfusion has been reported as the most successful fetal therapy procedure with 95% perinatal survival rate [8]. The overall survival rate after this antenatal treatment procedure varies with experience of center, development of fetal anemia before 20 weeks of gestation, and occurrence of fetal hydrops [9]. The presence of fetal hydrops during the first IUT reduces the success of the treatment. Lindenburg et al. reported the perinatal outcome of 491 fetuses who underwent 1422 intrauterine intravascular transfusion procedure during the antenatal period. They demonstrated that perinatal survival rate was 83% and 95% in hydropic and non-hydropic fetuses, respectively [10]. Although IUT contributes to the reduction of perinatal mortality, concerns about the neurological morbidities associated with this procedure have been considered only in a few studies [11]. Fetal intracranial hemorrhage as a short-term neurological morbidity was reported by Ghi et al. for the first time in 2003 [12]. They described four cases with intracranial hemorrhage related to the fetal anemia (two immune hydrops due to Rh D alloimmunization, two monochorionic twins complicated with the death of the cotwin). Consistently with the case currently reported, each of the cases related to Rh alloimmunization had very low initial hemoglobin values in the first IUT (1.2 g/dl and 1.6 g/dl, resp.). They suggested that disruption of intracranial vessels may be responsible in the pathophysiology of brain injury in severe anemic fetuses and noticed 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 [13]. In addition to the previously reported two cases, they described a case of periventricular leukomalacia and a case of unilateral ventriculomegaly that was noticed after the first IUT. They speculated that hypoxia/ischemia and the hyperdynamic circulation in fetal anemia cause the brain vessel disruption that leads to intracranial hemorrhage. They also considered that altered coagulation due to IUT might be responsible for intracranial hemorrhage. In our case, the initial and posttransfusion platelet values were detected in the normal range (154000/μl and 163000/μl, resp.), and there was no sign of increasing bleeding time such as excessive bleeding from the umbilical 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), and 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 have a beneficial effect on preventing the hemorrhagic complication 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 [14]. They reported three cases of intracranial hemorrhage involving cerebellum that two of them were 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 suggested 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 gestational week of the first IUT in the presence of Rh(D) alloimmunization and posttransfusion intracranial hemorrhage is not specific only the infratentorial region of the brain. Also it has been suggested that, in pregnancies complicated with the severe fetal hemolytic disease, an initial extremely low value of hematocrit (≤15%) should be increased gradually for the effect on preventing the hemorrhagic complication of this transfusion volume to avoid sudden fluctuations in cerebral blood flow may be helpful to prevent this complication.

Consent
Written informed consent was obtained from the patient to publish this case report.

Disclosure
No author received any specific grant from any funding agency in the public, commercial, or nonprofit sectors. The abstract of this study was presented as poster presentation during the 16th World Congress in Fetal Medicine 25–29 June 2017.

Conflicts of Interest
The authors declare that there are no conflicts of interest regarding the publication of this article.

References


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