

Hemolytic Disease of the Fetus and Newborn due to Intravenous Drug Use

Kara B. Markham, MD¹ Scott R. Scrape, MD² Mona Prasad, DO¹ Karen Q. Rossi, RN³
Richard W. O’Shaughnessy, MD¹

¹ Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, Columbus, Ohio

² Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, Ohio

³ Department of Obstetrics and Gynecology, Mount Carmel Health System, Columbus, Ohio

Address for correspondence Kara B. Markham, MD, Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, 395 W 12th Ave, 5th Floor/Columbus, OH 43210 (e-mail: kara.markham@osumc.edu).

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Abstract

Keywords

- ▶ hemolytic disease
- ▶ fetus
- ▶ newborn
- ▶ red blood cell
- ▶ alloimmunization
- ▶ intravenous drug use
- ▶ opiate abuse

Objectives The objective is to present a pregnancy complication associated with intravenous drug use, namely, that of red blood cell alloimmunization and hemolytic disease of the fetus and newborn.

Methods An observational case series is presented including women with red blood cell alloimmunization most likely secondary to intravenous drug abuse

Results Five pregnancies were identified that were complicated by red blood cell alloimmunization and significant hemolytic disease of the fetus and newborn, necessitating intrauterine transfusion, an indicated preterm birth, or neonatal therapy.

Conclusions As opioid abuse continues to increase in the United States, clinicians should be aware of the potential for alloimmunization to red blood cell antibodies as yet another negative outcome from intravenous drug abuse.

Opiate abuse is an epidemic in the United States. Drug overdose death rates have skyrocketed in the last decade, with death rates due to prescription opioid pain relievers quadrupling between 1999 and 2010.¹ This same time period also showed a nearly twofold increased risk in deaths due to heroin, a rate that then doubled again between 2010 and 2012.¹ Data regarding use are more difficult to obtain as such information usually relies upon self-report. In pregnancy, death due to illicit substances is relatively uncommon, but ~4.4% of women report use of non-medicinal drugs, with opioids noted to be the second most commonly abused substance.^{2,3} Much of this use is initiated as abuse of nonmedically indicated prescription pain pills, but heroin abuse is increasing in the setting of increased legislation limiting opiate prescriptions. Accordingly, the incidence of neonatal abstinence syndrome increased from 1.20 to 3.39 per 1,000 hospital births per year from 2000 to 2009.⁴

Beyond the risk of neonatal abstinence syndrome, there are several other complications and comorbidities associated with opioid use in pregnancy. Preterm birth, poor fetal

growth, and intrauterine fetal demise are more common in the setting of opioid abuse, and the risks of withdrawal from narcotics have been well documented.⁵ Drug abuse is also commonly associated with mental health disease, social problems, and financial issues. Beyond this, hepatitis C, hepatitis B, and human immunodeficiency virus (HIV) are commonly encountered in this population due to intravenous drug use and needle sharing. We present here another pregnancy complication associated with intravenous drug use, namely, that of red blood cell alloimmunization and hemolytic disease of the fetus and newborn (HDFN).

Methods and Materials

We present an observational case series of patients with red blood cell alloimmunization and a history of intravenous drug use identified at the Ohio State University (OSU) Wexner Medical Center between 2011 and December 1, 2015. Permission to retain and review patients’ data was obtained from

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the Ohio State University Biomedical Institutional Review Board before proceeding with this study. All patients denied having red blood cell antibodies in prior pregnancies or any previous children diagnosed with HDFN. Furthermore, each patient reported receiving all medically indicated Rh immune globulin (RhIG) injections during prior pregnancies, and they all denied a history of blood transfusions.

All laboratory testing was performed at The Ohio State University Medical Center using guidelines established by the American Association of Blood Banks.⁶ An antibody titer of $\geq 1:32$ at our institution is considered to be critical for most antibodies. Collected data included basic demographic information, maternal medical history (including infections with hepatitis C, hepatitis B, and/or HIV), maternal obstetric history, and indirect antiglobulin test results (antibody screening and titers). Pregnancy outcomes were collected including middle cerebral artery (MCA) Doppler results, specifics regarding intrauterine transfusions or other interventions for HDFN, and gestational age at delivery. Neonatal outcomes were obtained as well, including blood typing, red blood cell antigen status, and cord blood direct antiglobulin test results.

Results

Selected demographic data and pregnancy outcomes are outlined in ► **Table 1**. We have included patients who required in utero therapy, preterm birth due to concerns about fetal anemia, or neonatal therapy. Two additional cases were identified with low antibody titers (anti-C in one patient and anti-D in the other patient) and no diagnosis of HDFN.

Case 1

Patient 1 was a 26-year-old G4P2012 who was found to have anti-D and anti-C antibodies with an antihuman globulin titer of 1:32 at 9^{0/7} weeks of gestation. The father of the baby was not available for blood type screening, but determination of fetal Rh (D) status by maternal plasma cell-free fetal DNA analysis revealed that the fetus was Rh + . The patient underwent fetal MCA Doppler velocimetry every 2 weeks starting at 18^{5/7} weeks, with normal peak systolic velocities (PSVs) documented until 32^{6/7} weeks when the fetus developed polyhydramnios, an increased liver length, and an increased heart size with abnormal MCA Doppler assessment ((PSV of 76.87 cm/s consistent with 1.68 multiples of the median (MoM)). The patient was counseled at length and declined cordocentesis and intrauterine transfusion. She ultimately received antenatal corticosteroids and underwent a cesarean delivery for repetitive late fetal heart rate decelerations, delivering a 1,995-g male neonate. The neonate had an initial hemoglobin level of 10.0 g/dL at the time of delivery and developed significant hyperbilirubinemia soon thereafter. He underwent two exchange transfusions and received intravenous immunoglobulin (Carimune 6%) therapy three times during his hospital course.

Case 2

Patient 2 was a 24-year-old G2P0101 who presented at our institution at 29^{0/7} weeks with hydrops fetalis secondary to alloimmunization to Rh(D) red blood cell antigens. Her obstetric

Table 1 Selected demographic data and outcomes

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|--|--|---|---------------------------------|--|--|
| Blood type | O – | A Rh – | B Rh – | O – | A Rh – |
| Antibody | Anti-D, anti-C | Anti-D | Anti-D, anti-C | Anti-D, anti-C | Anti-D, anti-C, anti-E, anti-Fy ^a |
| History of IV drug use? | Yes | Yes | Yes | Yes | Yes |
| Current drug use? | Methadone | Buprenorphine | Methadone | Buprenorphine | Illicit narcotics |
| Hepatitis C infection? | No | Yes | No | Yes | Yes |
| Antibodies in prior pregnancy? | No | No | No | No | NA |
| Prior neonate/fetus with HDFN? | No | No | No | No | NA |
| RhIG in previous pregnancies? | Yes, per patient report | Yes, per patient report | Yes, per patient report | Yes, per patient report | NA |
| History of blood transfusion? | No | No | No | No | No |
| Fetal/neonatal blood type and antigen status | O + , C antigen + | A Rh + | O + , C antigen – | O + , C antigen + | O + , C antigen +, E and Fy ^a antigen status undeterminable |
| Pregnancy complications | Hydrops fetalis at 32 ^{6/7} wk, opted for delivery | Hydrops fetalis at 29 ^{0/7} wk | HDFN at 30 ^{4/7} wk | HDFN at 32 ^{6/7} wk, opted for delivery | HDFN at 19 ^{0/7} wk |
| Fetal/neonatal treatment | Neonatal exchange transfusions, IVIG therapy, and phototherapy | Seven intrauterine transfusions | Three intrauterine transfusions | Neonatal IVIG and phototherapy | Seven intrauterine transfusions |

Abbreviations: HDFN, hemolytic disease of the fetus and newborn; IV, intravenous; IVIG, intravenous immunoglobulin; RhIG, Rh immune globulin.

history included a prior vaginal delivery at 30 weeks of gestation of a 1,588-g male neonate with documented O-negative blood type. She was initially found to have anti-D antibodies in the first trimester of the current pregnancy, although antibody titers were not obtained. Per the patient's report, she had an ultrasound approximately 1 month prior to evaluation at OSU, at which time no concerns were noted. She then had an ultrasound 9 days prior to transfer to our hospital, with visualization of fetal ascites. A follow-up ultrasound 7 days later revealed worsening fetal ascites with interval development of fetal scalp edema, prompting transfer to OSU. On arrival at our institution, the presence of anti-D antibodies was confirmed with an antihuman globulin titer of 1:512. Ultrasound here showed fetal ascites, a small pericardial effusion, diffuse skin edema, and elevated PSVs on MCA Doppler evaluation (bedside ultrasound, actual PSV values not recorded), consistent with hydrops fetalis secondary to HDFN. The patient underwent cordocentesis on hospital day #2 showing an initial hemoglobin level of 2.8 g/dL with subsequent intrauterine transfusion of red blood cells resulting in a posttransfusion hemoglobin level of 5.9 g/dL. During that hospitalization, she underwent additional intrauterine transfusions on hospital days #3, #6, #9, and #16. Prior to the fifth transfusion, the fetal skin edema was noted to have resolved and afterwards a hemoglobin level of 15.4 g/dL was achieved. Given the improved clinical picture, she was discharged to home at 31^{1/7} weeks of gestation, but she was seen for additional intrauterine transfusions at 33^{2/7} weeks of gestation and 35^{5/7} weeks of gestation. She ultimately delivered a 5#10-oz neonate at 37^{4/7} weeks of gestation following spontaneous rupture of membranes. Details regarding this delivery and the neonatal hospital course are not known because the patient delivered at another hospital.

Case 3

Patient 3 was a 24-year-old G3P2002 who was found to have anti-D and anti-C antibodies with an antihuman globulin titer of 1:16 at 13 weeks of gestation. The father of the baby was not available for blood type screening, but determination of fetal Rh (D) status by maternal plasma cell-free fetal DNA analysis was inconclusive on two occasions. Her antibody levels increased to an antihuman globulin titer of 1:64 at 23^{3/7} weeks of gestation. The patient underwent fetal MCA Doppler velocimetry every week starting at 24^{1/7} weeks, with normal PSVs documented until 30^{4/7} weeks at which time the fetus developed abnormal MCA Doppler assessment (PSV of 67.3 cm/s consistent with 1.64 MoM). Given the concerns for HDFN, the patient underwent cordocentesis showing an initial hemoglobin level of 3.7 g/dL with subsequent intrauterine transfusion of red blood cells resulting in a posttransfusion hemoglobin level of 11.0 g/dL. Two additional transfusions were performed at 31^{4/7} weeks of gestation and 32^{5/7} weeks of gestation. We planned on another transfusion at 34^{4/7} weeks of gestation, but the patient was found to have significant oligohydramnios. She was counseled at length at that time and opted to undergo delivery. She subsequently underwent a repeat cesarean delivery at 34^{5/7} weeks of gestation, delivering a 2,800-g female neonate. The initial neonatal hemoglobin level was 13.4 g/dL, and no additional transfusions were required during her hospital course.

Case 4

Patient 4 was a 30-year-old G4P3003 who was found to have anti-D and anti-C antibodies with an antihuman globulin titer of 1:64 at 12^{2/7} weeks of gestation. Of note, although the patient had documented hepatitis C with viremia, she reported access to a sterile needle supply and denied a history of needle sharing. The father of the baby was not available for blood type screening, but determination of fetal Rh(D) status by maternal plasma cell-free fetal DNA analysis revealed that the fetus was Rh + . The patient underwent fetal MCA Doppler velocimetry every 2 weeks starting at 18^{0/7} weeks, with normal PSVs documented until 32^{1/7} weeks at which time the fetus developed abnormal MCA Doppler assessment (PSV of 77.6 cm/s consistent with 1.75 MoM). She was counseled at that time about the theoretic concerns for hepatitis C vertical transmission with cordocentesis and intrauterine transfusion, ultimately opting for delivery after antenatal corticosteroid administration. She delivered vaginally at 32^{6/7} weeks, delivering a 1,860-g female neonate. The initial neonatal hemoglobin level was 12.0 g/dL. The baby received two doses of intravenous immunoglobulin (Carimune 6%) therapy and phototherapy for hyperbilirubinemia. The hemoglobin level nadired at 7.8 g/dL but then stabilized such that no transfusions were required during her hospital course.

Case 5

Patient 5 is a 22-year-old G1P0 who was found to have multiple red blood cell antibodies with antihuman globulin titers as noted at 11^{6/7} weeks of gestation: anti-D, 1:512; anti-C, 1:16; anti-E, 1:32; and Anti-Fy^a, 1:16. The father of the baby was not available for blood type screening, but determination of fetal Rh(D) status by maternal plasma cell-free fetal DNA analysis revealed that the fetus was Rh + . The patient underwent a fetal MCA Doppler velocimetry assessment at 19^{0/7} weeks revealing an elevated PSV of 51 cm/s consistent with >2 MoM. Given the concerns for HDFN, the patient underwent cordocentesis showing an initial hemoglobin level of 4.4 g/dL with subsequent intrauterine transfusion of red blood cells resulting in a posttransfusion hemoglobin level of 13.4 g/dL. She received six additional transfusions during the pregnancy, the last of which was performed at 29^{5/7} weeks and was complicated by persistent fetal bradycardia necessitating delivery via an urgent cesarean delivery. She delivered a 985-g female neonate with a birth hemoglobin level of 11.4 g/dL. The neonate required phototherapy for hyperbilirubinemia and received two doses of intravenous immunoglobulin (Carimune 6%) therapy. The neonatal hemoglobin level nadired at 5.6 g/dL at 1 month of life, and the baby ultimately received three red blood cell transfusions in the first 35 days of life.

Discussion

We present here a pregnancy complication owing to intravenous drug use, specifically the occurrence of red blood cell alloimmunization and HDFN. This is a potentially serious complication with implications for both the patient and the fetus/neonate. In the only other reported case series of four women (five pregnancies) with alloimmunization due to needle sharing, outcomes were very poor, with hydrops

fetalis identified in four of the five fetuses and only two of the five babies surviving to delivery.⁷ With up-to-date monitoring and treatment, however, we obtained excellent outcomes in this population. The patients presented here developed significant HDFN, requiring intrauterine transfusion, an indicated preterm birth, and/or neonatal therapy, but they all delivered a live-born, healthy neonate.

An injection of as little as 0.5 to 1.0 mL of D-positive red blood cells will cause antibody formation in 50% of Rh-negative recipients.⁸ In fact, the majority of cases of alloimmunization in pregnancy occur due to fetomaternal hemorrhage of less than 0.1 mL.⁹ It has been estimated that 41% of intravenous drug users report sharing needles and/or paraphernalia,¹⁰ and the state of Ohio currently does not endorse a formal needle-exchange program.

Red blood cell alloimmunization has greatly decreased since the introduction of RhIG as part of routine prenatal/postpartum care. The occurrence of alloimmunization to the D antigen decreases from 16% in untreated women after two pregnancies to 0.1% with appropriate use of RhIG in Rh-negative patients with incompatible fetuses.⁹ Patients exposed to incompatible red blood cell antigens via intravenous drug abuse obviously do not benefit from this preventative measure.

In this case series, we excluded all patients who could have been alloimmunized in another manner, although the major weakness of this case series is that we cannot completely eliminate other causes for sensitization. This issue is particularly applicable as this patient population may not always report an accurate history. For example, patient 3 denied a history of sharing needles, but her hepatitis C infection suggested otherwise.

Not only is intravenous drug use a previously unreported mechanism for HDFN, but also this patient population presents several other issues that must be considered when deciding on treatment options. First of all, patients with a history of opiate abuse frequently have financial and social issues, factors that can greatly impact their ability to comply with recommendations for frequent visits. For example, these patients may even be incarcerated during their pregnancy. Second, anesthetic options may be complicated at the time of procedures such as cordocentesis or intrauterine transfusion due to patients' altered perception of pain and resistance to the effects of opioid pain relievers. Finally, hepatitis C, hepatitis B, and/or HIV infections are relatively common in this population. While such infections are not contraindications to performing an amniocentesis, cordocentesis, or intrauterine transfusion, there are case reports of vertical transmission attributed to such procedures.^{11,12} Infected patients must be counseled about this risk. With development of concerns for HDFN at an early gestational age (i.e., <32–34 weeks of gestation), the benefits of intrauterine transfusion and prolonged gestation likely outweigh the risk of maternal-to-child transmission, but delivery may be a more appropriate intervention as the gestational age increases.

Screening for substance abuse is recommended as part of routine prenatal care, and antibody screening is included in routine prenatal laboratory testing. While no specific additions to care are recommended based on the information presented here, clinicians should be aware of the potential for alloimmunization to red blood cell antibodies as yet another negative outcome from intravenous drug abuse.

Conflict of Interest

The authors have no conflicts of interest to report.

Synopsis

Red blood cell alloimmunization and HDFN can occur due to intravenous drug abuse.

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