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REVIEW ARTICLE

Intraventricular Hemorrhage in a Single Fetus of Dichorionic-Diamniotic Gestation: A Case Report and Review of Literature

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Abstract Intraventricular hemorrhage (IVH) is a serious complication of prematurity and is of high concern due to the risk of brain injury and in severe cases, death. We report the first case of IVH in a fetus of dichorionic-diamniotic pregnancy that worsened postnatally. Antenatally, magnetic resonance imaging confirmed a large IVH after ventricular abnormalities were detected by prenatal ultrasound (US). At birth, a grade IV IVH diagnosis was made and progressive ventricle dilatation was noted on weekly US. A ventriculoperitoneal shunt was placed and ventricle dilatation was slightly reduced, however, the IVH was essentially unchanged. The infant was discharged in stable condition at 12-weeks-old and chronic neurological dysfunction is expected. IVH is seen in complicated births of prematurity and antenatal US can inform an examiner if fetal IVH is present. It is important to identify IVH and provide immediate intervention to prevent disease worsening during the antenatal and postnatal period.

Keywords Intraventricular hemorrhage · Dichorionic-diamniotic · Pregnancy · Infant mortality · Women

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Background

Intracranial hemorrhage (ICH) is a common complication of prematurity, occurring in approximately 25–45% of neonates born prior to 32 weeks' of gestation or birth weights below the 10th percentile [1–3]. Of the subtypes of perinatal ICH, intraventricular hemorrhage (IVH) is the most prevalent with an incidence rate of 5.5 per 100,000 live term births [3, 4]. Improvements in fetal imaging have increased the identification of IVH in utero, however, limited data exists regarding the actual incidence of the potentially life-threatening complication during the antenatal period [5]. The etiologies of fetal IVH are broad with the most common being idiopathic, uteroplacental abnormalities, congenital disorders, maternal trauma, vascular malformations, complications of monochorionic twinning, and immune disorders [6, 7]. Of the immune disorders, alloimmune thrombocytopenia is the most common, occurring at a rate of 1 in 12, 500–25,000 births [8]. Identification of the underlying cause of fetal IVH is essential for maximizing fetal outcomes and reducing similar disease states in future pregnancies.

Twins are the most common type of multifetal pregnancy and occurr in approximately 1 in 60 pregnancies [9, 10]. Multifetal pregnancies are at a higher risk of preterm labor, uteroplacental abnormalities, and other antenatal complications that are associated with poor fetal outcomes [11–13]. Monochorionic twins are more likely to develop insufficient vascular anastomoses that may result in unbalanced inter-twin blood flow and eventual IVH, yet, dichorionic twins are still at risk due to cerebral vascular immaturity at birth [14–17]. In the absence of maternal complications during pregnancy, perinatal fetal IVH is frequently attributed to disturbances in cerebral blood flow and germinal matrix fragility leading to hemodynamic

instability and hemorrhage during childbirth [18, 19]. In utero, the causes of fetal IVH are more dynamic and interventions during prenatal care are needed to improve outcomes at birth [20, 21]. To the best of the authors' knowledge, few publications have discussed the identification of antenatal fetal IVH in dichorionic-diamniotic (di-di) twins. To provide a better understanding of fetal IVH in di-di twins, a case report will be presented that elaborates on the disease process, the recommended maternal/fetal management plan, and the expected outcomes of the infants as they develop.

Case

A 40-year-old African American woman, gravida 7 para 6, with a known di-di twin gestation, was referred to maternal–fetal medicine (MFM) at 25 weeks' gestation for evaluation of fetal abnormalities. Her past obstetric history was significant for advanced maternal age, gestational diabetes mellitus, anemia with sickle cell trait, and postpartum hemorrhage. The patient had no known history of fertility treatment or alloimmune thrombocytopenia. Her family history was significant for sickle cell trait and hypertension. Several social concerns were present, including a history of homelessness, a lack of prenatal care, frequent clinic cancellations, and a concern of prior drug abuse, however, toxicology screening was negative. TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes simplex virus) screening was performed and was negative for all organisms, except HSV-2 IgG positive. Current medications were ferrous sulfate, aspirin 81 mg, and folic acid. Her complicated pregnancy record is shown in Table 1.

Her first prenatal visit was at 12.2 weeks at an outside hospital, apart from MFM, at which her first ultrasound (US) denoted three intrauterine gestational sacs with the appearance of a trichorionic-triamniotic pregnancy. A subsequent US at 16.4 weeks demonstrated spontaneous reduction to twins with findings suggestive of an atrioventricular (AV) canal defect and thickened nuchal fold in fetus A and an intrauterine growth restriction (IUGR) in fetus B. Diagnostic testing for aneuploidy was recommended and declined. The patient was instructed on the importance of regular follow-up evaluations but did not return to the clinic until 25 weeks' gestation. At 25 weeks, she reported to MFM and US imaging confirmed an unchanged di-di twin pregnancy.

At 29.6 weeks, she was admitted to MFM for inpatient observation following severe nausea, dizziness, lethargy, and a diagnosis of preterm labor. Fetal magnetic resonance imaging (MRI) at 30.2 weeks (Fig. 1) was performed to evaluate the severity of fetal abnormalities. Fetus A had an estimated fetal weight (EFW) of 1554 g (49th percentile) and confirmed AV canal defect with possible overriding aorta. Fetus B had an EFW of 1230 g (6th percentile) and confirmed left intracranial hemorrhage in the parietal intraparenchymal and abutting the lateral wall of the left lateral ventricle (grade IV). US denoted single vertical pocket volumes of 4.52 cm and 3.10 cm for fetus A and B, respectively. Biophysical profiles (BPP) were 8/8 for fetus A and 6/8 (− 2 for absent breathing) for fetus B. A cesarean delivery (C-section) was scheduled for 34 weeks due to complicated IUGR, as described below, in the setting of di-di twin gestation.

At 31 weeks, fetus B developed moderate variability and approximately 2-min prolonged decelerations with an FHR baseline of 135 bpm (category II). Fetus B was nonreactive, and the largest amniotic fluid pocket was 1.8 cm. BPP was 8/8 for fetus A and 4/8 (− 2 for fluid and − 2 for movement) for fetus B. Umbilical artery resistance was elevated in fetus B, which was suggestive of IUGR. Emergent C-section was performed and fetus A (female; 1940 g) and fetus B (male; 1350 g) infants were transferred to the neonatal ICU for supportive management. Imaging of neonate B confirmed a grade IV left intracranial hemorrhage with cystic encephalomalacia and porencephalic changes. Weekly US denoted progressive lateral, third, and fourth ventricular dilation with effacement of visualized extra axial spaces, as well as, increasing cystic change of the periventricular white matter of neonate B (Fig. 2a). SNP Microarray analysis (Affymetrix Cytoscan HD) of neonate B revealed a normal male result with no genetic abnormalities. Imaging of neonate A confirmed an AV canal defect and a large patent ductus arteriosus. Cytogenetic testing demonstrated a female karyotype with Trisomy 21.

At 6-weeks-old, a left occipital ventriculoperitoneal (VP) shunt was inserted in neonate B for progressive worsening of ventricle dilatation and continued IVH evolution. At 11-weeks-old, neonate B was neurological stable, and US denoted only a slight post-operative decrease in ventricle dilatation with essentially unchanged cystic periventricular leukomalacia in the left cerebral hemisphere (Fig. 2b). Variable facial and lower extremity twitching was observed, and electroencephalography showed focal cerebral dysfunction with epileptiform potential. Prophylactic levetiracetam was initiated and spontaneous twitching improved. Neonate B was medically stable for discharge at 12-weeks-old and follow-up was scheduled at an outside hospital at the mother's request.

Table 1 Prior pregnancy record

Gravida/para		Gestational age	Sex	Delivery type	Weight (g)	Antenatal complications	Postnatal complications
1	1	39w0d	F	Spontaneous-vaginal	2698	Pre-eclampsia treated with magnesium sulfate	Postpartum hemorrhage
	2	39w0d	F	Spontaneous-vaginal	2698		
2	3	40w0d	M	Spontaneous-vaginal	2268	–	–
3	4	42w0d	F	Spontaneous-vaginal	4801	–	–
4	5	37w4d	F	Spontaneous-vaginal	3836	Limited prenatal care	–
5	6	37w4d	M	Spontaneous-vaginal	3836	6–7 cm dilation on admission	1st degree laceration
6	7	37w2d	F	Spontaneous-vaginal	3118	–	–
7	8	31w3d	F	Low transverse C-section	1940	Spontaneous reduction to twins; IUGR; Limited prenatal care; AMA	–
	9	31w3d	M	Low transverse C-section	1350		

Prior pregnancy record demonstrates several antenatal and postnatal complications during prior pregnancies. Of note, the first pregnancy was a di-di pregnancy with no fetal complications. The current pregnancy, Gravida 7, is presented herein

Discussion

Prior Reports

PubMed was searched using Boolean operators to identify prior case reports of antenatal fetal IVH in di-di twins. The parameters of the literature search process are shown in addendum I, Figure 1. Only two publications were identified that discussed fetal ICH in utero in di-di twins. Hines et al. [22] reported that a set of di-di twins demonstrated sonographic finding of echogenic material in the frontal horn at 18 weeks' gestation, which may be causative of IVH. Ultrasonography and fetal MRI at 20- and 22-weeks' gestation exhibited normal ventricular findings and both twins were normal at birth. Sanapo et al. [23] completed a review of fetal MRI and sonography performed at Children's National from 2008 to 2015 in Washington, DC and found one instance of a di-di twin fetus exhibiting imaging findings associated with IVH. MRI imaging at 33 weeks' gestation demonstrated grade IV, bilateral germinal matrix hemorrhages with cerebral ventricle sizes of left 15 mm, right 14 mm, third 5 mm, and fourth within normal limits in twin A. Twin B demonstrated no neurological abnormalities. C-section was performed at 35 weeks' gestation due to complications of preeclampsia. Neonatal MRI confirmed ventricular abnormalities in twin A with additional findings of a thin corpus callosum and cerebral white matter volume loss. Follow-up at 1 month denoted normal neurological development of twin A.

The two prior publications provide limited insight on di-di twin fetal IVH antepartum management and outcomes. Based on our extensive literature search process, we believe this case report is the first to describe antepartum management and fetal outcomes in detail in di-di twins with fetal antenatal IVH.

Intraventricular Hemorrhage

Fetal outcomes of IVH are dependent on the size and location of hemorrhage. Papile et al. [24] were the first to document grades of IVH using CT in premature infants while Volpe [25] modified the criteria 30 years later using the presence of parenchymal lesions as an indicator of disease severity. The differences in grading systems are minor and are meant to supplement one another, rather than replace. Volpe's grading system is as follows: Grade I—bleeding confined to the germinal matrix (5% mortality); Grade II—IVH occupying 10-50% of the ventricular area on parasagittal view (10% mortality); Grade III—IVH occupying $> 50\%$ of the ventricular area on parasagittal view (20% mortality); and Grade IV—periventricular venous hemorrhage (50% mortality) [25, 26] (Table 2). Retrospective studies have found that fetal outcomes for grades I–II are comparable to normal fetuses while neurological sequelae and risk of developmental complications rapidly increase in grades III–IV [21, 27]. Frequent imaging and grading of IVH in utero allow for disease progression monitoring and the development of a treatment plan that will

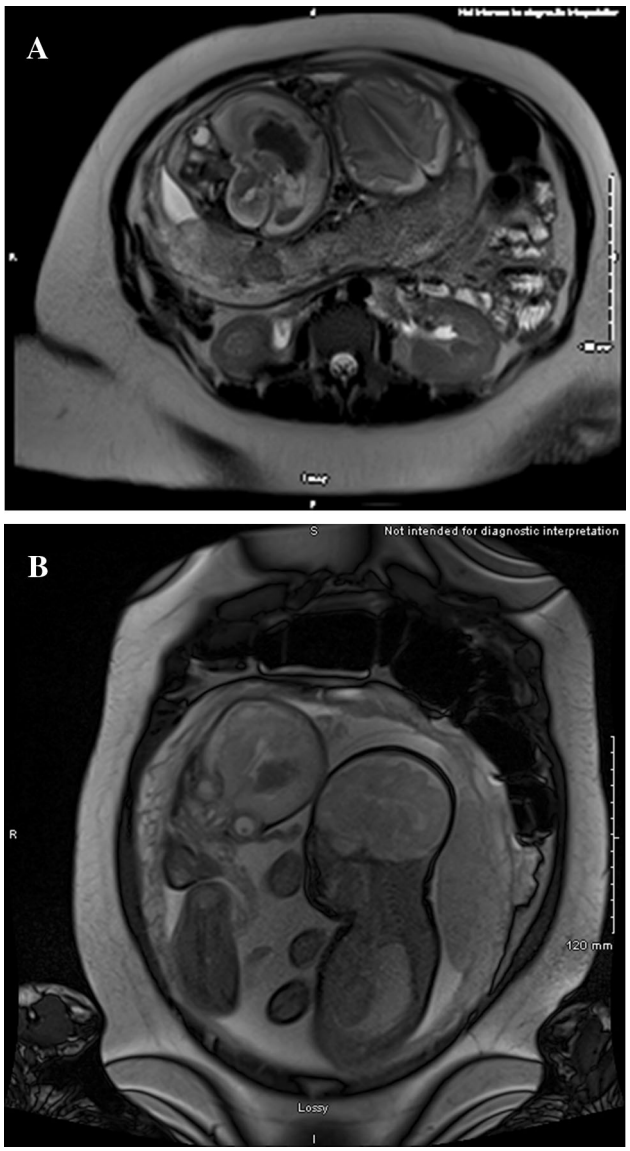

Fig. 1 Axial (**a**) and coronal (**b**) MRI of the mother at 30.2 weeks' gestation. Fetus B (anatomic right) has markedly dilated ventricular system with large, grade IVH measuring 2.2 × 2.9 × 4.3 cm in size. Periventricular hemorrhagic infarction was noted on the left with a midline shift to the right of approximately 2–3 mm related to mass effect from the IVH. Fetus A (anatomic left) has no evidence of neurologic abnormalities

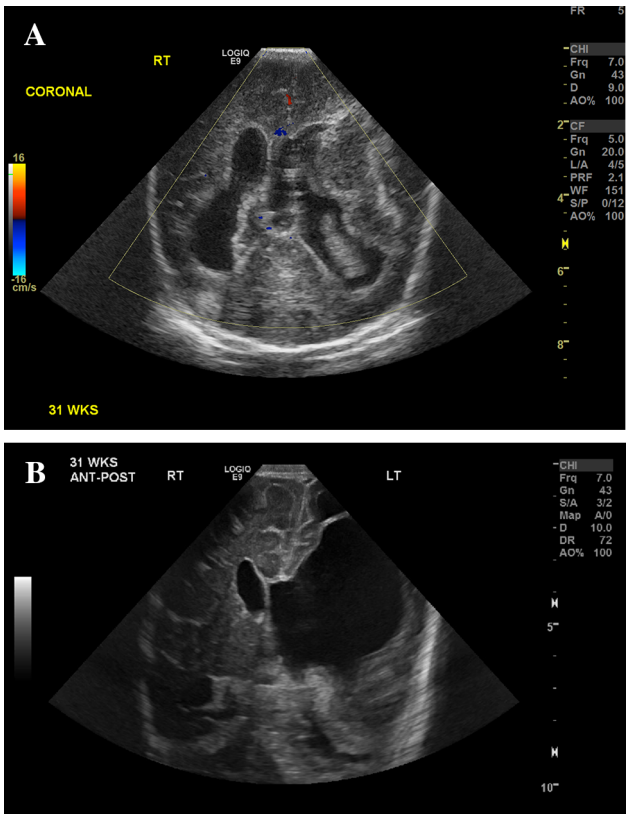

Fig. 2 Coronal US of the brain of neonate B. **a** At 1-day-old, extensive grade IV left germinal matrix hemorrhage. Left echogenic periventricular leukomalacia with cystic/liquefactive and porencephalic changes were noted. **b** At 11-weeks-old, postoperative changes from left VP shunt with slight decrease in the size of the left and right lateral ventricles are shown. No new ICH with continued evolution of prior left germinal matrix hemorrhage and associated periventricular parenchymal cystic change. Mass effect shift was noted to anatomical right in both (**a**, **b**)

maximize the health outcomes of the fetus. Low BPP values are not always indicative of acute, fetal complications and prior studies have demonstrated that low BPP values are closely associated with IVH [28]. Individual evaluation of BPP value changes should consider co-existing fetal complications when contemplating fetal management.

Mechanism of Pathophysiology

The pathophysiologic mechanisms of fetal IVH are numerous due to the complex, multifactorial nature of the disorder. Most instances of IVH occur secondary to an inciting event, however, there have been few reports of IVH arising de novo [29]. Even when primary IVH is suspected, post-mortem examination usually suggests a secondary origin based on the anatomical defect causing ventricular instability [8, 30]. Secondary IVH manifests when there is inherent fragility of the germinal matrix, profound fluctuations in cerebral blood flow, or in coagulation disorders [18]. Neurological development is a tightly regulated process that involves various cells of ependymal origin. The germinal matrix is a highly cellular and vascularized region located next to the caudate nucleus and beneath the ventricular ependyma that functions as a source of immature cells [31]. Neurodevelopment, especially during the second trimester, is a rapid event that requires a rich vascular network to supply migrating neurons and associated neuroglia [32]. As immature cells migrate radially from the caudate nucleus, the interface between blood and brain may be compromised, resulting in

Table 2 Volpe's grading system of IVH: Volpe's grading system of IVH modified from Papile et al. original classification of IVH based on hemorrhage severity by computerized tomography scan

Grade	Features	Mortality (%)
I	Bleeding confined to germinal matrix	5
II	IVH occupying 10–50% of ventricular area on parasagittal view	10
III	IVH occupying > 50% of ventricular area on parasagittal view	20
IV	Periventricular venous hemorrhage	50

Volpe's grading system suggest that parenchymal lesions (grade IV) should be considered separately. Volpe's grading system was used herein

hemorrhage. Frailty of the developing blood–brain barrier (BBB) has been shown to arise from reduced fibronectin in the basal lamina, decreased glial fibrillary acidic protein expression in astrocytes, and diminished paucity of pericytes [33, 34]. The mechanisms causing a weakened BBB may be numerous, but the outcome is always hemorrhage.

Acute, rapid disturbance in cerebral blood flow is a common mechanism of injury of IVH [35]. Normal, fetal cerebral blood flow (CBF) is characterized by a stable pattern with equal peak and trough of systolic and diastolic flow velocity. A positive correlation is evident when modeling systolic peak velocity of the middle cerebral artery and gestational age using linear regression [36]. Fetal peak systolic CBF increases with gestational age, which reflects the growing metabolic needs of neurodevelopment. Gradual increases in fetal CBF are adequately compensated by progressive strengthening of the BBB, and minor fluctuations in flow velocity are tolerated. Any significant disturbance of fetal CBF, such as occurs in sepsis, hypertension, respiratory distress, or trauma can overwhelm the structural integrity of the cerebral vascular causing hemorrhage at the most vulnerable vascular location, i.e. germinal matrix. Any acute increase, as occurs in trauma or prolonged rise in fetal CBF as seen in preeclampsia, predisposes the fetus to IVH during both the antepartum and postpartum period [37].

Fetal complications from coagulation disorders are significant and increase mortality, however, it is uncertain if coagulopathy is a direct cause of IVH. Like fetal systolic peak CBF, coagulation factors linearly increase with gestational age and hypocoagulability is a common complication of prematurity [3]. Nevertheless, fetal coagulation disorders remain a predisposing factor to IVH due to their presence in at-risk fetuses. Thrombocytopenia is the most common neonatal coagulopathy with an incidence of 1–5% in all newborns, 6–8% in newborns of prematurity, and 22–35% in all newborns admitted for intensive care [38, 39]. Common complications of fetal thrombocytopenia are intracranial hypertension with increased tissue and capillary hydrostatic pressure, which may cause hemodynamic instability in the germinal matrix [40]. The presence of coagulopathy is most likely a co-morbidity associated with prematurity, but additional evidence is needed to determine if coagulopathy is a direct cause or predisposing factor of IVH.

Few genetic aberrations have been identified that may contribute to the development of fetal IVH. Of those identified, dominant mutations in the gene coding for type IV collagen alpha-1 (COL4A1) may cause highly penetrant cerebrovascular disease, such as IVH [41]. Type IV collagen is a principal component of the basement membrane and several gene variants have been shown to disrupt protein folding, resulting in endothelial cell dysfunction and leaky capillaries [42]. Interestingly, COL4A1 variants, especially in the triple helix-forming domain region, have been found in few case reports of fetal cerebral hemodynamic instability in di-di twins. Giorgio et al. [43] reported a 34-year-old female with a de novo COL4A1 mutation that birthed full-term, di-di twins with severe encephalopathy. Neonatal genetic sequencing established the autosomal dominant inheritance pattern of the maternal COL4A1 mutation. Bilguvar et al. [44] searched for COL4A1 variants in 41 preterm infants presenting with IVH and discovered a heterozygous duplication in a set of di-di twins. Genetic sequencing of the mother and maternal grandmother confirmed their heterozygous carrier status for the COL4A1 mutation, however, neither had a history of IVH, prematurity, or any vascular instability. The di-di twins were premature at 29 weeks' gestation and pregnancy was complicated by chorioamnionitis, coagulase-negative sepsis, and respiratory distress syndrome. The data reviewed herein suggests that COL4A1 mutations may increase the risk of IVH and associated hemorrhage in di-di twins, but the data is statistically insignificant, and more research is needed to evaluate the role of COL4A1 in fetal IVH.

Neonatal Outcomes

The clinical outcome of neonates with IVH developed at time of delivery has been found to be dependent on several factors including developmental age at delivery, maturity of the brain, underlying etiology, severity of the bleed, presence of concurrent white matter injury, and other complications. Premature neonates with severe hemorrhage have the highest mortality rate, reported to be

approximately 50%, while those with moderate and small hemorrhage have a mortality rate of 15 and 5%, respectively [3, 24–26]. IVH accompanied by white matter injury carries a strong association with Cerebral Palsy, impaired mental and motor development, and visual dysfunction [45]. Neonates with IVH that avoided prolonged periods of raised intracranial pressure do not develop cognitive impairment thereby emphasizing the importance of early surgical intervention [46]. Once IVH has been diagnosed at the time of delivery, it is imperative to reduce further damage by correcting acidosis, repleting intravascular volume, and maintaining hemodynamic stability [47].

During the period following large IVH, the neonate should be monitored by ultrasound to evaluate for post-hemorrhagic hydrocephalus as it occurs in approximately 29% of neonates with IVH at 2–6 weeks after initial hemorrhage [47]. This hydrocephalus is thought to be caused by inflammation and obstruction of the subarachnoid villi leading to impaired CSF resorption. Moreover, low-grade IVH has mixed outcomes, where extremely low birthweight neonates with Grade I or II IVH either had no significant difference or only slightly higher rates of CP or mental or motor impairment compared with neonates without IVH [48]. Thus, clinical outcomes of IVH are variable and can only be determined on a case-by-case basis.

Summary

Intraventricular hemorrhage is the most common form of fetal ICH, primarily affecting preterm infants less than 32 weeks' gestation. The etiology of IVH is extensive with the most common cases being the result of germinal matrix instability following premature, vaginal birth. Little data is available elaborating on the course of pregnancy and neonatal outcomes of IVH identified in di-di twins in utero, therefore, we believe we are the first to report such an instance. Our patient was referred to MFM after a first trimester US demonstrated di-di twins in the context of prior complicated pregnancies. US by MFM denoted findings associated with fetal ventriculomegaly and follow-up MRI confirmed presence of IVH in one fetus. The use of fetal MRI has become increasingly important in clarifying fetal abnormalities following initial detection by US. Around 31 weeks' gestation, the IVH fetus developed severe oligohydramnios and FHR tracings were non-assuring. Two preterm newborns were delivered by C-section and were admitted to NICU for observation. The maternal, post-operative course was uncomplicated, and she was discharged against medical advice. Twin A was delivered in mild respiratory distress with clinical findings suggestive of Down's syndrome. Cytogenetic analysis confirmed Trisomy 21 and developmental outcomes consistent with Down's syndrome are expected. Twin B was delivered in acute distress and imaging confirmed grade IV IVH. Weekly US demonstrated progressive ventricular enlargement with white matter changes. Despite mild facial abnormalities, microarray analysis revealed a normal male result. Mortality is estimated at 50% for twin B with a 90% likelihood of neurological sequelae during development.

This case report describes an unusual case of antenatal fetal IVH in di-di twins. One prior case study described an instance of IVH detected using ultrasound in one di-di twin, however, subsequent imaging demonstrated regression of the hemorrhage. Sanapo et al. provided a review of a di-di twin with antenatal fetal IVH, however, no discussion was presented on the clinical course. Therefore, this is a rare case report of di-di twin fetal IVH that was diagnosed in utero and confirmed postpartum. We hope this case study may be used as a guide for future clinicians who encounter instances of antenatal fetal IVH in di-di twins.

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Compliance with ethical standards

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