Can J Diabetes 43 (2019) 550–553

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Case Report

Bilateral Renal Vein and Inferior Vena Cava Thrombosis Associated With Fetal Vascular Malperfusion and Maternal Diabetes

Beth Ellen Brown MD [a,*]; Craig Midgen MD [b]; Kathleen O'Brien MD [c]; Walid El-Naggar MD [a]; Jillian Coolen MD [d]

[a] Division of Neonatal–Perinatal Medicine, Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada
[b] Department of Pathology, Dalhousie University, Halifax, Nova Scotia, Canada
[c] Department of Diagnostic Radiology, Dalhousie University, Halifax, Nova Scotia, Canada
[d] Division of Maternal Fetal Medicine, Department of Obstetrics and Gynaecology, Dalhousie University, Halifax, Nova Scotia, Canada

Key Messages

- Maternal diabetes is a risk factor for fetal vascular malperfusion, which can lead to severe adverse perinatal outcomes.
- A high index of suspicion is required for diagnosis of possible consequences.

ARTICLE INFO

Article history:
Received 14 March 2019
Received in revised form
25 July 2019
Accepted 31 July 2019

Introduction

Fetal vascular malperfusion (FVM), previously known as fetal thrombotic vasculopathy, refers to a group of placental lesions indicating reduced or absent perfusion of the villous parenchyma by the fetus (1). It has been postulated that the Virchow triad of stasis, hypercoagulability and endothelial damage are contributing factors to the development of FVM (1). Although the underlying etiology of FVM remains unclear, pre-existing maternal diabetes is a known risk factor. FVM can lead to severely adverse perinatal outcomes, including fetal growth restriction, thromboembolic events and intrauterine fetal demise (2–4). We report a case of FVM resulting in bilateral renal vein thrombosis (RVT) with inferior vena cava involvement, presenting as acute nonimmune hydrops fetalis in a moderately preterm infant born to a mother with type 1 diabetes mellitus (T1DM).

Case Report

A 29-year-old primigravida with longstanding T1DM was admitted at 31^{+2} weeks gestation with decreased fetal movement and an atypical nonstress test in the setting of 7 to 10 days of challenging blood sugar control. The pregnancy was planned and preconception glycated hemoglobin (A1C) was 7.1%. She had no known diabetic sequelae and was managed with continuous subcutaneous insulin infusion. To this point, the pregnancy had been uncomplicated and glycemic control had been excellent, with an A1C of 5.9% at 24 to 28 weeks gestation.

At the time of admission, fetal assessment demonstrated an appropriately grown fetus with normal Doppler findings, but new-onset polyhydramnios. A few days later, there was worsening of polyhydramnios and evidence of premature cervical change; therefore, she received a therapeutic amniocentesis, 2 doses of betamethasone and an insulin infusion to optimize glycemic control. She was discharged from hospital after 6 days with ultrasound surveillance planned twice weekly.

At 33^{+4} weeks gestation, she presented again with decreased fetal movement. Ultrasound revealed nonimmune hydrops fetalis as demonstrated by ascites and generalized skin edema, and acute fetal compromise as demonstrated by a biophysical profile of 2/8 and abnormal fetal Doppler findings, including reversed end-diastolic flow in the umbilical artery and a reversed A wave in the

* Address for correspondence: Beth Ellen Brown MD, Division of Neonatal–Perinatal Medicine, Department of Pediatrics, IWK Health Centre, Dalhousie University, 5980 University Avenue, Halifax, Nova Scotia B3K 6R8, Canada.
E-mail address: be.brown@mun.ca

https://doi.org/10.1016/j.jcjd.2019.07.152

ductus venosus, a sign of impending fetal demise. An emergency caesarean section was performed to deliver a depressed female with notable generalized edema. Significant resuscitation, including endotracheal intubation, was required for stabilization. Apgar scores were 3, 6 and 8 at 1, 5 and 10 minutes, respectively. The cord arterial pH was 7.05.

The infant was admitted to the neonatal intensive care unit for ongoing management. Initial laboratory investigations demonstrated significant metabolic acidosis with severely elevated lactate, hypoglycemia (1.0 mmol/L), anemia (hemoglobin 99 g/L), thrombocytopenia (platelets 75×10^9/L), coagulopathy (international normalized ratio 2.03, partial thromboplastin time 48.6 seconds, fibrinogen 1.54 g/L), transaminitis (alanine aminotransferase 388 U/L, aspartate aminotransferase 2,563 U/L) and acute renal impairment (creatinine 126 μmol/L, urea 5.2 mmol/L). Hematuria and oliguria were noted.

Initial imaging included chest X-ray, echocardiogram, cerebral ultrasound and abdominal ultrasound. The abdominal ultrasound demonstrated ascites and bilaterally large kidneys with abnormal echogenicity, high-resistance arterial flow, diastolic reversal and no venous flow. The absence of colour Doppler flow coupled with reduced corticomedullary differentiation and the presence of internal linear echogenicities supported the diagnosis of renal vein thrombosis in the left kidney. The axial view of the right kidney demonstrated a thrombus extending from the inferior vena cava into the renal vein. Together, these findings confirmed the diagnosis of bilateral RVT (Figure 1A). The proximal inferior vena cava also showed a thrombus (Figure 1B). On gross placental examination, the placenta was large for gestational age (492 g; 311 to 464 g expected for 33 weeks), with a normally inserted, normally coiled, unremarkable-appearing umbilical cord. The umbilical cord vessels were of normal caliber and void of thrombi. On section, the parenchyma of the disc appeared largely unremarkable with the exception of focal areas of firm red-purple consolidation. Further examination demonstrated subtotally occlusive mural thrombi within the chorionic plate and stem villous vasculature (Figure 2A), and regional terminal villous changes, including vascular endothelial and stromal karyorrhexis and vascular involution, consistent with FVM (Figure 2B).

Management included anticoagulation and supportive care. Ultimately, due to declining renal function, peritoneal dialysis was instituted. Thrombophilia work up was negative in both parents. The infant remained in hospital for approximately 5 months. At present, she is doing well, despite end-stage renal disease, and awaiting renal transplant.

Discussion

RVT is the most common noncatheter-related cause of thromboembolic events in neonates (5). Its exact mechanism of onset and progression within the neonatal population remains unclear. Reported risk factors include perinatal asphyxia, sepsis, dehydration, polycythemia, cyanotic congenital heart disease, maternal antiphospholipid antibody syndrome and maternal diabetes (6). Although FVM has not been reported in the literature as a classic risk factor, our case, and a case reported by Giacchetti et al in 2017 (7), highlight the importance of FVM as a risk factor for fetal/neonatal RVT. Giacchetti et al, however, recognized unilateral RVT in an asymptomatic neonate without a history of maternal diabetes (7). FVM is a recently emphasized entity, but remains

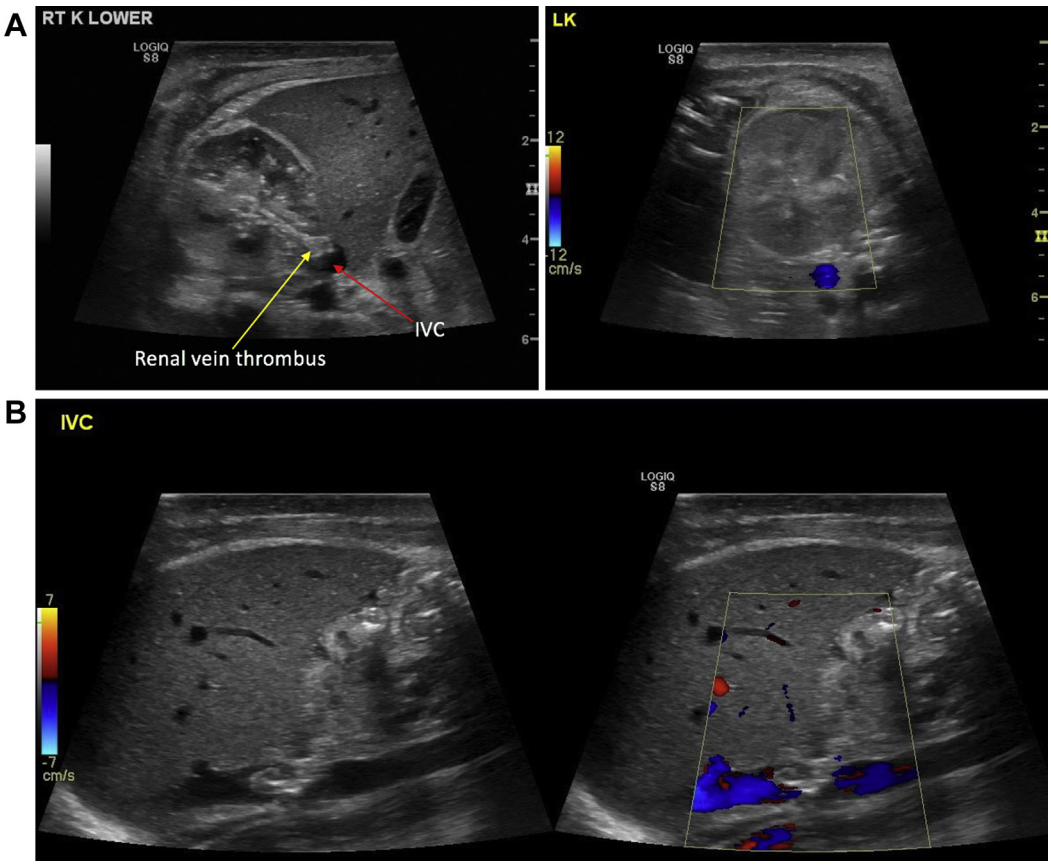

Figure 1. (A) Right and left kidneys demonstrating reduced corticomedullary differentiation and increased cortical echogenicity. The right kidney showed thrombus extension from the inferior vena cava (IVC) into the right renal vein, and the left kidney showed absence of colour Doppler flow and increased linear echogenicities, suggesting thrombi within the smaller renal veins. (B) Ultrasound image with and without Doppler of the inferior vena cava demonstrating a partially occlusive thrombus.

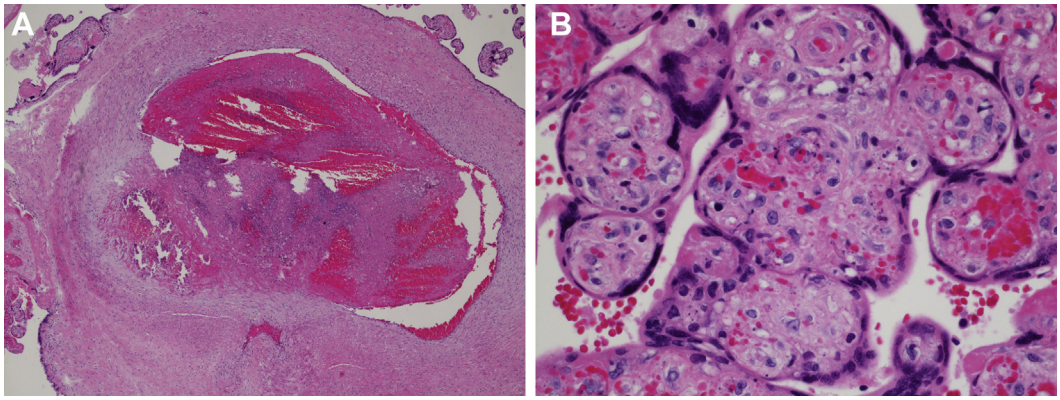

Figure 2. (A) Partially occlusive stem vessel thrombus with early calcification (hematoxylin–eosin stain; original magnification ×40). (B) Terminal villus with vascular endothelial and stromal karyorrhexis and extravasation of red cell fragments (hematoxylin–eosin stain; original magnification ×200).

under-recognized clinically. Although obstructed umbilical cord flow remains the predominant risk factor, other contributing factors include fetal cardiac insufficiency, hyperviscosity and inherited or acquired thrombophilias (1). Maternal diabetes is an important and often underappreciated risk for FVM, given other more common complications of diabetes in pregnancy, including hypertension, preterm delivery, large-for-gestational age infants, caesarean delivery and other neonatal morbidities, such as neonatal hypoglycemia and hyperbilirubinemia (8). The mechanism by which maternal diabetes causes FVM is not fully known. However, the development and functioning of the fetal placental vascular system are vulnerable to the maternal diabetes environment, which influences changes in the placental vasculature (increased angiogenesis, altered permeability and altered junctional maturity) (9). As such, it may be postulated that these differences in the placental vasculature, coupled with the hypercoagulable state, generally associated with pregnancy, are the contributing factors for FVM in this setting. In conjunction with the 3 pillars of the Virchow triad (stasis, hypercoagulability and endothelial damage), the process of fetal response to FVM by activation of the coagulation system, coupled with alterations in the fetal–placental circulation, could be hypothesised as the inciting event leading to the fetal bilateral RVT seen in our case (10).

Further contributing to the under-recognition of FVM is the lack of specific, reliable ultrasound criteria to establish the diagnosis prenatally (2). Although prenatal diagnosis may not be feasible, keeping a high index of suspicion in at-risk populations, particularly women with pre-existing diabetes, can serve to identify potential complications (such as fetal thrombosis) early, and provide opportunity for intervention before intrauterine fetal demise. In the case described, retrospective review of the ultrasound study performed 2 days before delivery showed enlargement and increased echogenicity of the fetal kidneys. Moreover, recognizing FVM as a potential complication of maternal diabetes and sending the placenta for pathologic examination, enabling a postnatal diagnosis, is extremely valuable as it provides neonatal care providers with valuable information to rule out the significant neonatal complications associated with this entity. These complications include, but are not limited to, intestinal atresia, cerebral hemorrhage, growth restriction and thromboembolism affecting the liver, heart, central nervous system and, as demonstrated in this case, the kidneys (2–4,7). Although such complications are relatively uncommon, the clinical significance can be profound. A large, prospective study is needed to comprehensively examine FVM and the associated fetal/neonatal complications, including long-term follow up of health and development, so we may obtain further insight into the true incidence and epidemiology of this condition, to heighten clinical awareness and recognition, and to better understand the implications of FVM on fetal/neonatal prognosis, both short and long term.

Although proper glycemic control of maternal diabetes helps prevent adverse perinatal complications, in our case excellent glycemic control, as indicated by an A1C level of 5.9%, did not prevent the development of bilateral RVT. The explanation of this novel finding is not clear to us, but it warrants further investigation and research.

To our knowledge, this is the first reported case of FVM involving bilateral renal vein and inferior vena cava thrombosis presenting as acute nonimmune hydrops fetalis and fetal compromise in the setting of maternal diabetes. It illustrates the importance of maternal diabetes as a risk factor for FVM, and highlights the possible association between FVM and fetal/neonatal thrombosis. In addition, it demonstrates the potential profound consequences maternal diabetes and FVM may have on pregnancy, fetal and neonatal outcomes. Care providers for pregnant women with diabetes need to be aware of this entity so that the placenta and fetal end organs—that could be affected by FVM—can be monitored more closely antenatally and postnatally. Herein lies opportunity for future research endeavors to enable prenatal diagnosis, management and prevention of FVM.

Acknowledgments

The authors are grateful to the patient's parents, who provided written informed consent for publication of this report and the accompanying images.

Author Disclosures

Conflicts of interest: None.

Author Contributions

B.E.B. carried out the literature search and initial manuscript preparation. B.E.B., J.C., W.E.N. and C.M. were the main moderators of the manuscript. C.M. and K.O.B. provided the supporting images. All authors read and approved the final manuscript.

References

1. Redline RW, Ravishankar S. Fetal malperfusion, an update. APMIS 2018;126:561–9.
2. Lepais L, Gaillot-Durand L, Boutitie F, et al. Fetal thrombotic vasculopathy is associated with thromboembolic events and adverse perinatal outcome but not

with neurologic complications: A retrospective cohort study with 54 cases with a 3-year follow-up of children. Placenta 2014;35:611–7.
3. Lian DWQ, Lam JCM, Aung ACL, Li FX, Chang KTE. Intestinal atresia occurring in association with placental fetal thrombotic vasculopathy: A case report with literature review. Pediatr Devel Pathol 2013;16:28–31.
4. Heider A. Fetal vascular malperfusion. Arch Pathol Lab Med 2017;141:1484–9.
5. Khule S, Massicotte P, Chan A, Mitchell L. A case series of 72 neonates with renal vein thrombosis. Data from the 1-800-NO-CLOTS Registry. Thromb Haemost 2004;92:729–33.
6. Brandao LR, Simpson EA, Lau KK. Neonatal renal vein thrombosis. Semin Fetal Neonatal Med 2011;16:323–8.
7. Giacchetti L, De Gaudenzi M, Leoncini A, Ferrucci E, Pezzoli V, Albisetti M. Neonatal renal and inferior vena cava thrombosis associated with fetal thrombotic vasculopathy: A case report. J Med Case Rep 2017;248:2–5.
8. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2018;42(Suppl. 1):S1–325.
9. Leach L, Taylor A, Sciota F. Vascular dysfunction in the diabetic placenta: Causes and consequences. J Anat 2009;215:69–76.
10. Taweevisit M, Thorner PS. Massive fetal thrombotic vasculopathy associated with excessively long umbilical cord and fetal demise: Case report and literature review. Pediatr Devel Pathol 2010;13:112–5.