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CASE REPORT

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Fetal umbilical vein thrombosis associated with fetal bartter syndrome: an unusual case report and literature review

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Abstract

Background Bartter syndrome (BS) is a rare autosomal recessive renal disease. There are relatively few reports on fetal Bartter syndrome, but it has been documented that the condition can increase the incidence of prematurity and hypovolemia. Umbilical vein thrombosis (UVT) is a rare obstetric complication that poses a serious threat to fetal safety, potentially leading to acute fetal distress and even intrauterine fetal death. Consequently, early identification and intervention of UVT are crucial.

Case presentation We present a case of an emergency cesarean section prompted by ultrasound findings of intrahepatic segment of umbilical vein thrombosis and polyhydramnios. After birth, the newborn was admitted to the Department of Neonatology for observation and further treatment due to persistent, uncorrected hypokalemia. Genetic testing diagnosed the infant with Bartter syndrome type 4b. We hypothesize that the umbilical vein thrombosis and polyhydramnios in this case may be associated with fetal Bartter syndrome.

Conclusion This case highlights a suspected instance of umbilical vein thrombosis and polyhydramnios potentially linked to fetal Bartter syndrome. Currently, the causes of umbilical vein thrombosis primarily focus on abnormalities in umbilical cord structure or mechanical injury to the cord, with few cases involving fetal genetic conditions. The purpose of this report is to enhance medical professionals' understanding of Bartter syndrome and to consider it as a possible cause of fetal umbilical vein thrombosis and polyhydramnios. Further research should explore the link between fetal Bartter syndrome, umbilical vein thrombosis, and polyhydramnios. Additionally, strengthening case collection and analysis will help accumulate experience, optimize management strategies, and improve maternal and fetal outcomes.

Keywords Fetal umbilical vein thrombosis, Bartter syndrome, Polyhydramnios, Prenatal ultrasound, Case Report

Background

Fetal umbilical vein thrombosis is a rare pregnancy complication that can increase the risk of adverse perinatal outcomes and may even lead to intrauterine fetal death. Bartter syndrome is a rare autosomal recessive kidney disease caused by specific gene mutations. These mutations result in impaired salt reabsorption, primarily manifesting as secondary hyperaldosteronism, accompanied by hypokalemia, hypochloremic metabolic alkalosis [1]. We report a rare case of emergency cesarean section due to fetal umbilical vein thrombosis complicated by

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polyhydramnios. The preterm infant was subsequently diagnosed with Bartter syndrome due to persistent hypokalemia after birth. We speculate that rare conditions such as Bartter syndrome may contribute to the occurrence of polyhydramnios and fetal umbilical vein thrombosis.

Case presentation

A 28-year-old woman, gravida 2, para 1, was admitted to the hospital at 30 + 4 weeks' gestation with complaints of irregular contractions for one week. The patient had a history of induced labor at 32 weeks due to intrauterine fetal demise. At that time, aside from polyhydramnios, no significant abnormalities were identified in the fetal structure or amniocentesis results. The induction of labor was performed at another hospital, where neither an autopsy nor a placental pathological examination was conducted, leaving the underlying cause of the fetal demise undetermined. During her initial prenatal check-up at 12 + 5 weeks at our hospital, she was found to have a lupus anticoagulant detection coefficient of 1.29 (weakly positive) and a positive antinuclear antibody test with a titer of 1:100. Tests for ACL antibody and β2GP1 were negative. Given her adverse obstetric history, she was managed with low-dose aspirin (75 mg daily) and low-molecular-weight heparin (4000 U daily) from the first trimester to prevent thrombosis. Her Nuchal Translucency (NT) scan, non-invasive prenatal testing (NIPT), and comprehensive fetal ultrasound were all normal. At 25 weeks, she was diagnosed with gestational diabetes mellitus, which was effectively managed. One week before admission, she experienced irregular abdominal distension, and an ultrasound indicated cervical shortening. She was admitted due to gestational diabetes, polyhydramnios, and threatened preterm labor. Upon admission, obstetric ultrasound revealed an amniotic fluid depth of 9.2 cm (normal range: 2–8 cm), an amniotic fluid index (AFI) of 26.3 cm (normal range: 5–24 cm), and an umbilical artery S/D ratio of 2.19. Magnesium sulfate was administered to inhibit contractions, and dexamethasone was given to promote fetal lung maturity. On the ninth day of hospitalization, a repeat ultrasound revealed slight thickening and poor sound transmission in the intrahepatic segment of the fetal umbilical vein, indicating a blood flow defect (Fig. 1a). Additionally, tortuous and dilated vessels were observed at the fetal abdominal wall (Fig. 1b) and bladder insertion site (Fig. 1c), with collateral circulation noted. A faint venous catheter-like flow spectrum was detected. middlecerebral artery(MCA) measurements were: S/D = 2.66, RI = 0.62, PI = 1.06, PSV = 46.90 cm/s, and EDV = 17.64 cm/s. These findings suggested thrombosis in the intrahepatic segment of the fetal umbilical vein and a decreased MCA pulsatility index. After preoperative evaluation, the patient delivered a male neonate weighing 1570 g via emergency caesarean section. The amniotic fluid was clear, and Apgar scores were 9 at 1 min, and 10 at both 5 and 10 min. The umbilical cord was twisted with 20 loops, showing congestion and edema near the umbilical area (Fig. 2). Due to

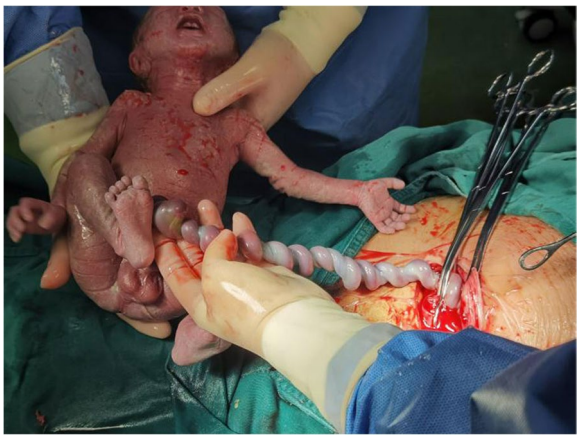

Fig. 2 The umbilical cord of premature infant was obviously congestion and edematous

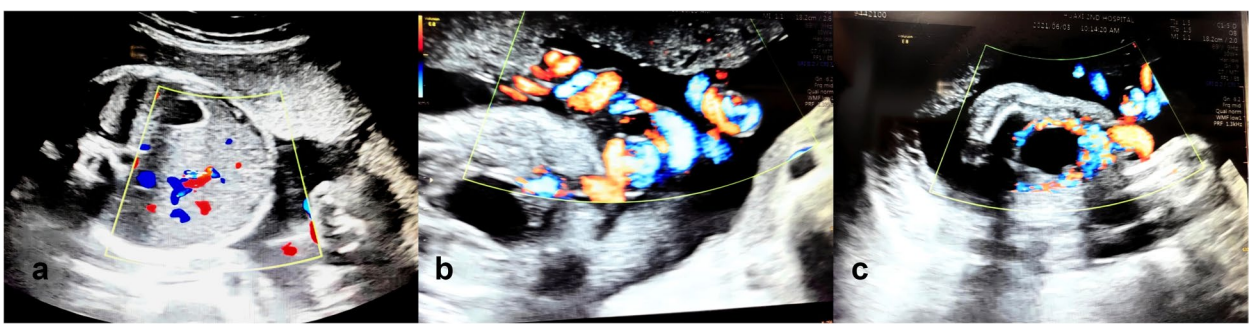

Fig. 1 **a** Intrahepatic segment of umbilical vein blood flow signal filling defect **b** Tortuous and dilated vessels at the fetal abdominal wall **c** Tortuous and dilated vessels running on both sides of the bladder

the urgency of the emergency cesarean section, the placenta was not submitted for pathological examination.

Post-delivery, the newborn was transferred to the neonatal department for observation due to premature birth. During hospitalization, the infant was moved to the pediatric nephrology department for recurrent hypokalemia, hyponatremia, hypochloremia, and metabolic alkalosis. Blood gas analysis showed a pH of 7.475 and a potassium level of 2.4 mmol/L,and the potassium level was lower than normal. Additional tests revealed renin levels above 500.00 uIU/ml, aldosterone over 100 ng/dl, fibrinogen degradation products at 87.76 ug/ml, and a D-dimer of 3.25 ug/ml. The above measured values were higher than normal. A 24-h urine test showed potassium at 8.4 mmol, sodium at 15.5 mmol, and chloride at 21.1 mmol. Whole-exome genetic testing confirmed a diagnosis of Bartter syndrome, either type 4b or type 3. Neither parent exhibited clinical manifestations of Bartter syndrome. Genetic testing revealed that the father carried deletions in CLCNKA exons 8–20 and CLCNKB exons 1–7, while the mother had a deletion in CLCNKB exons 1–20. The child developed Bartter syndrome, likely type 4b, due to the combination of these genetic deletions. Currently, the child is in good health, with normal growth and development comparable to peers of the same age.

Discussion and conclusions

Umbilical vascular thrombosis is a serious complication that occurs during the second and third trimesters of pregnancy, posing significant risks to fetal safety in utero. Umbilical vascular thrombosis is a rare clinical occurrence, with an incidence rate of approximately 0.08% in the general pregnant population. Among high-risk pregnant women, the incidence increases to around 0.4% [2]. Current literature identifies several primary causes of umbilical vascular thrombosis, including abnormal umbilical vascular anatomy, intrauterine infection, fetal coagulation abnormalities, and maternal blood sugar irregularities [3]. Impaired fetal circulation due to umbilical vascular thrombosis can lead to fetal growth restriction, fetal distress, and even fetal death [4]. Upon the detection of umbilical vascular thrombosis, fetal monitoring should be intensified, and timely termination of the pregnancy should be considered.

Ultrasound is currently the preferred method for prenatal examination to detect fetal umbilical vascular abnormalities. On two—dimensional ultrasound images, the normal umbilical cord should be shown as two umbilical arteries and one umbilical vein. During the examination, the free segment of the umbilical vascular should be scanned sequentially. If poor sound transmission or weak echo filling is observed in a segment of the umbilical vascular lumen, along with a filling defect in the blood flow signal, the possibility of umbilical vascular thrombosis should be highly suspected. Ruan Aihua [5] et al. found that in cases of umbilical vascular thrombosis with fetal distress, ultrasound could detect an increase in the resistance indices of the fetal umbilical artery (including PI, RI, and S/D). There may also be a disappearance or reversal of umbilical artery end-diastolic blood flow, a decrease in the resistance indices of the fetal middle cerebral artery (PI, RI, and S/D), a fetal biophysical score of less than 7, and abnormal fetal heart rates. Currently, advanced high-resolution blood flow ultrasound technology can enhance the diagnostic rate of umbilical vascular thrombosis [6].

Bartter syndrome is a rare autosomal recessive renal disease with an estimated annual incidence of 1.2 cases per million individuals [7]. At present, the disease is classified into five types based on the underlying genetic mutation, with types 1–4 being autosomal recessive and type 5 being X-linked recessive [8]. Additionally, Bartter syndrome can be categorized by the time of onset: prenatal or neonatal Bartter syndrome occurs during the fetal or neonatal period, while classical Bartter syndrome manifests in infancy or early childhood [9]. Prenatal Bartter syndrome is characterized by excessive fetal polyuria, which typically presents as polyhydramnios between 18 and 30 weeks of gestation [10]. Polyhydramnios is a critical prenatal indicator of the disease, as more than half of patients with type 3 Bartter syndrome have been reported to exhibit this as a primary pregnancy symptom [11]. Bartter syndrome type 4b or type 3 related proteins are responsible for chloride ion reabsorption on the basement membrane side, and their inactivation reduces chloride and sodium reabsorption, activating the renin–angiotensin–aldosterone system, which leads to potassium loss and renal fibrosis [12]. Researchers suggest that analyzing the chloride concentration in amniotic fluid can aid in prenatal diagnosis [13], allowing for early detection and improved pregnancy monitoring and neonatal care. Excessive polyuria is the most prominent symptom of Bartter syndrome in the neonatal period, and can even lead to hypovolemia. Untreated newborns may die of dehydration and electrolyte disorders.

In our case, the pregnant woman experienced polyhydramnios during her first pregnancy, which resulted in fetal demise despite normal examination findings. In her current pregnancy, polyhydramnios recurred. After birth, the newborn was admitted for persistent hypokalemia, and genetic testing confirmed Bartter syndrome type 4b. Similar cases have been documented in the literature. Dane B et al. [14]reported a case of prenatal Bartter syndrome diagnosis in a woman with a history of polyhydramnios. Her previous pregnancies showed polyhydramnios, the baby was born at 28 weeks of gestation and died of unknown reason. During a subsequent

pregnancy, the woman again developed polyhydramnios, with elevated chloride levels in the amniotic fluid and decreased maternal serum potassium levels. Potassium chloride was administered to maintain normal potassium levels. The fetus was delivered at 32 weeks of gestation and symptoms of polyuria emerged at 4 weeks post-birth, and was subsequently diagnosed with antenatal Bartter syndrome. Another case reported by Gómez de la F CL et al. [15] described a pregnant woman who underwent a cesarean section at 35 weeks of gestation due to severe polyhydramnios. After birth, the newborn exhibited polyuria and required medical intervention to restore electrolyte balance. Despite the absence of genetic testing, the diagnosis was made based on the history of severe polyhydramnios during pregnancy and postpartum findings of polyuria, electrolyte imbalances, severe hypokalemia, and alkalosis. The newborn also developed persistent metabolic disturbances and renal calcinosis. In this case, deep sensorineural hearing loss will point to type IV BS.These cases underscore the potential association between polyhydramnios and Bartter syndrome, highlighting the importance of vigilant maternal and fetal monitoring and the consideration of genetic factors in similar situations.

We speculate that the umbilical vein thrombosis in our case may be related to Bartter syndrome. Based on genetic testing, we believe polyhydramnios was caused by fetal polyuria, leading to reduced fetal blood volume and a hypercoagulable state, ultimately resulting in thrombosis. Two potential mechanisms are proposed: hemoconcentration caused by excessive polyuria, which increases blood viscosity and promotes a hypercoagulable state, and severe electrolyte imbalances, such as hypokalemia and metabolic alkalosis, which may disrupt vascular homeostasis and endothelial function, indirectly increasing thrombotic risk. Other factors, such as the markedly hypercoiled umbilical cord (twisted 20 loops) and a history of gestational diabetes mellitus, may have contributed to thrombosis, but these were less likely to be primary causes, as gestational diabetes was well-controlled and anticoagulant therapy was provided to address potential atypical obstetric antiphospholipid syndrome. Although the excessively twisted umbilical cord could have impaired blood flow, fetal heart rate and movement monitoring showed no abnormalities, suggesting it was not the main factor. Therefore, we hypothesize that Bartter syndrome, through mechanisms such as polyuria-induced hemoconcentration and electrolyte imbalances, played a significant role in the development of umbilical vein thrombosis in this case.

To sum up, obstetricians should thoroughly review the patient's medical history during pre-pregnancy examinations and prenatal care. If a history of adverse pregnancy outcomes is identified, they should consider the possibility of fetal chromosomal abnormalities and other genetic diseases in the pregnant woman. Prenatal ultrasound is a crucial tool for monitoring the fetus in utero and detecting umbilical vascular abnormalities. Sonographers should meticulously inquire about and verify any significant diagnoses and carefully scan the fetal umbilical cord structure and its course, comparing findings with previous results to minimize the risk of missed or incorrect diagnoses of umbilical vascular thrombosis. This case highlights the importance of enhanced maternal and fetal monitoring during the perinatal period in cases of polyhydramnios. Regular assessment of maternal and fetal conditions is essential, and follow-up plans should be adjusted as necessary. Chromosomal abnormalities should be considered, and prenatal interventions should involve consultations with neonatology and pediatric nephrology specialists. In the future maternal management, genetic testing of important recessive genetic diseases of prenatal parents should be established. For neonates with polyhydramnios and preterm birth, it is vital to monitor urine output, weight, electrolytes, and blood gases after birth to detect and manage prenatal and neonatal Bartter syndrome effectively. In emergency situations such as umbilical vascular thrombosis and placental dysfunction, pregnancy should be promptly terminated to reduce the risk of adverse outcomes associated with umbilical vascular thrombosis. Further research should explore the link between fetal Bartter syndrome, umbilical vein thrombosis, and polyhydramnios. Additionally, strengthening case collection and analysis will help accumulate experience, optimize management strategies, and improve maternal and fetal outcomes.

Abbreviations

BS	Bartter syndrome
UVT	Umbilical vein thrombosis
NT	Nuchal Translucency
NIPT	Non-invasive prenatal testing
AFI	Amniotic fluid index
S/D ratio	The ratio of peak systolic velocity to end diastolic velocity
MCA	Middlecerebral artery
RI	Resist index
PI	Pulsatility index
PSV	Peak systolic velocity
EDV	End diastolic velocity

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Z, Case summary and article writing X, designed the work J, Provide case data and Provide opinions to the article.

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Data availability
The data that support the findings of this study are available on request from the corresponding author, jia, upon reasonable request.

Declarations

Ethics approval and consent to participate
The need for approval was waived and written consent was obtained.

Consent for publication
Written informed consent to publish this information was obtained from study participant. Documentation of the written consent will be provided to the journal upon request.

Competing interests
The authors declare no competing interests.

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