Early View Article: Online published version of an accepted article before publication in the final form.

Journal Name: Journal of Case Reports and Images in Obstetrics and Gynecology

Type of Article: Case Report

Title: Antenatal bilateral renal vein and vena cava thrombosis in dichorionic twin pregnancy

Authors: Moez Kdous, Marwene Brahem, Oussema Khlifi, Mohamed Khrouf, Monia Ferchiou, Fethi Zhioua

doi: To be assigned

Early view version published: September 10, 2015.

How to cite the article: Kdous M, Brahem M, Khlifi O, Khrouf M, Ferchiou M, Zhioua F, Antenatal bilateral renal vein and vena cava thrombosis in dichorionic twin pregnancy. Journal of Case Reports and Images in Obstetrics and Gynecology. Forthcoming 2015.

Disclaimer: This manuscript has been accepted for publication. This is a pdf file of the Early View Article. The Early View Article is an online published version of an accepted article before publication in the final form. The proof of this manuscript will be sent to the authors for corrections after which this manuscript will undergo content check, copyediting/proofreading and content formatting to conform to journal’s requirements. Please note that during the above publication processes errors in content or presentation may be discovered which will be rectified during manuscript processing. These errors may affect the contents of this manuscript and final published version of this manuscript may be extensively different in content and layout than this Early View Article.
TYPE OF ARTICLE: Case Report

TITLE: Antenatal bilateral renal vein and vena cava thrombosis in dichorionic twin pregnancy

AUTHORS:
Moez Kdous¹, Marwene Brahem², Oussema Khlifi³, Mohamed Khrouf⁴, MoniaFerchiou⁵, FethiZhioua⁶

AFFILIATIONS:
¹MD, Department of Obstetric and Gynecology, Aziza Othmana Hospital, Tunis, Tunisia. Email ID:moezkdous@yahoo.fr
²Department of Obstetric and Gynecology, Aziza Othmana Hospital, Tunis, Tunisia. Email ID:brahamm@voila.fr
³Department of Obstetric and Gynecology, Aziza Othmana Hospital, Tunis, Tunisia. Email ID:khlifi.o@laposte.tn
⁴Department of Obstetric and Gynecology, Aziza Othmana Hospital, Tunis, Tunisia. Email ID:medkrouf@yahoo.fr
⁵Department of Obstetric and Gynecology, Aziza Othmana Hospital, Tunis, Tunisia. Email ID:moniafechiou@voila.fr
⁶Department of Obstetric and Gynecology, Aziza Othmana Hospital, Tunis, Tunisia. Email ID:zhiouafethi@voila.fr

CORRESPONDING AUTHOR DETAILS
Moez Kdous,
Department of Obstetric and Gynecology,
Aziza Othmana Hospital,Kasba, Tunis Postal Code: 1008, Tunisia.
Phone Number: 00216 21 852 683,
Fax number: 00216 71 260 327
Email: moezkdous@yahoo.fr
Short Running Title: none

Guarantor of Submission: The corresponding author is the guarantor of submission.
TITLE: Antenatal bilateral renal vein and vena cava thrombosis in dichorionic twin pregnancy

ABSTRACT

Introduction
Antenatal renal vein thrombosis is a rarely described diagnostic finding, with variable consequences on kidney function.

Case Report
We present the unusual case of a dichorionic twin pregnancy in 34 weeks of gestation with one affected fetus, showing already intrauterine a bilaterallyhyperechoic kidneys with a left kidney increased in size and cardiotocographic signs of fetal distress, while dichorionic male co-twin was healthy. At birth, there was no heartbeat of the affected fetus despite resuscitation. Clinical examination of the stillborn showed that both kidneys were bulky. At autopsy, it was a stillborn boy, with enlarged hemorrhagic kidneys, and thrombosis of the renal and adrenal veins, extending to the inferior vena cava, with no sign of fetal hydrops except for a moderate pleural effusion. Histological examination confirmed the presence of hemorrhagic infarction by massive bleeding with thrombosis of both renal veins and supra-renal vena cava. The postnatal thrombophilia investigations revealed a heterozygous mutation in the MTHFR gene with no associated hyperhomocysteinemia.

Conclusion
There are still many unresolved issues regarding antenatal vein thrombosis. Diagnostic possibilities and prognostic probabilities still show large discrepancies.

Keywords: Thrombosis of renal veins; Inferior vena cava thrombosis; Antenatal thrombosis, Twin pregnancy.
INTRODUCTION

Antenatal renal vein thrombosis is a rarely described diagnostic finding, with variable consequences on kidney function. Its prevalence ranges from 2.2 to 50/100 000 births [1]. Renal vein thrombosis is particularly serious and can occur insidiously during pregnancy. It is difficult to define a group of patients at risk or a standardized approach to monitoring, surveillance and prevention, given the small number of cases. In the antenatal period, the condition is usually unknown to sonographers and it is mainly diagnosed after birth. We present the unusual case of a dichorionic twin pregnancy in 34 weeks of gestation with one affected fetus.

CASE PRESENTATION

The mother was a nulliparous female without medical family or personal history. The pregnancy was after in vitro fertilization. Two embryos were implanted, resulting in a twin dichorionic diamniotic pregnancy. Her 1st and 2nd trimester ultrasounds were normal. A 3rd trimester ultrasound, performed at 33 weeks, detected an abnormality in the first twin's scan, which consisted of bilateral hyperechoic kidneys with the left kidney increased in size; no abnormalities had been noted in the previous scans [Figure 1]. This renal abnormality was not initially linked with disease of the renal veins. After birth by Cesarean section, the first twin had acute fetal distress and no heartbeat whereas the second twin was clinically normal. Clinical examination of the stillborn showed that both kidneys were bulky. Birth weight was 2060g (5th percentile for the term). A prenatal examination had not evoked the renal pathology; therefore, a diagnosis of late-onset renal-vein thrombosis was suspected as a possible cause of per partum death. An autopsy revealed enlarged hemorrhagic kidneys, distension of the Gerota fascia [Figure 2], and thrombosis of the renal and adrenal veins, extending to the inferior vena cava, with no sign of fetal hydrops except for a moderate pleural effusion.
Histological examination confirmed the presence of hemorrhagic infarction from a massive bleed with thrombosis of both renal veins and the supra-renal vena cava [Figure 3, 4, 5]. The stillborn’s placenta weighed 315 g (10th percentile). A comparative study between both placentas showed that the stillborn’s had moderate central fibrinoid necrosis and congestion of the villous veins without thrombosis, whereas the second twin’s placenta was normal. There were no signs of placental vasculopathy in either case. The cord of the stillborn’s placenta had a marginal insertion.

A review of thrombophilia was carried out in the parents and the neonate including the search for Factor V or Factor II mutations, protein S deficiency, antithrombin III, and protein C, as well as a mutation 2 in the MTHFR gene; revealed a heterozygous mutation in the MTHFR gene with no associated hyper-homocysteinemia in either the mother or neonate.

**DISCUSSION**

Neonatal renal vein thrombosis was first described by Rayer in 1837 and is a rare event that went undiagnosed for many decades until its discovery during surgery or post-mortem. Its incidence varies from 0.5‰ of admissions to neonatal intensive care units to 0.5% in autopsy series [2]. Its presence in a dichorionic twin pregnancy obtained by in vitro fertilization does the originality of our case report. Some cases may occur in the antenatal period. Most authors agree that thrombosis begins in the small veins of the renal parenchyma and expands towards the large venous trunks up to the renal vein or inferior vena cava. Furthermore, compression of the left renal vein by the aorta is also linked to a higher prevalence of thrombosis of the left renal vein, in its unilateral form [3]. Any maternal and/or fetal condition promoting hyperosmolarity may cause the development of renal vein thrombosis. The risk factors for thrombosis can be classified into three types: biological, amnestic and clinical. Biological risk factors include: protein C, protein S and antithrombin-III deficiencies; Factor II or Factor V mutations; hyperhomocysteinemia linked to a homozygous mutation in the MTHFR gene; homozygous sickle cell disease; anti-cardiolipin antibodies; and circulating lupus anticoagulant in the mother’s blood and
transmitted to the fetus in utero [4]. Identified anamnestic and clinical risk factors include: caesarean section; male gender; per-natal anoxia; maternal history of thrombosis; pregnancy-induced hypertension; gestational diabetes; premature birth; dehydration; shock; and any cause of increased osmolarity. Nearly 50% of cases will demonstrate thrombophilia [5].

In the case reported here, the mother and child were both heterozygous for the MTHFR gene mutation with no associated hyperhomocysteinemia. Nevertheless, the prevalence of heterozygous MTHFR mutation is estimated around 30 to 40 % in the general population, therefore it seems as an unlikely cause. A marginal umbilical cord insertion was present in our patient, providing an anatomic predisposition to umbilical blood flow restriction. Few manuscripts address the relationship between placental fetal vascular thrombosis and renal vein thrombosis. If expanded to include other visceral lesions, manuscripts highlighting placental fetal vascular thrombosis and cerebral, pulmonary and/or hepatic thromboemboli/infarction can be added to this relatively short list [6].

Typical postnatal symptoms of renal vein thrombosis include an abdominal mass, bloody urine, and thrombocytopenia. The diagnosis is achieved though ultrasound. Doppler ultrasound is the gold standard to confirm renal vein obstruction and to detect its extension to the contralateral kidney, inferior vena cava, and adrenal glands. The ultrasound findings depend on the stage of thrombosis. Initially, the interlobar and interlobular furrows appear hyperechoic. Quickly, the kidney becomes globular and hyperechoic with hypoechoic pyramids, with the eventual loss of cortico-medullar differentiation. Doppler (done in postnatal studies) reveals the disappearance of venous flow, an elevated resistance index in the artery, with, occasionally, the appearance of reverse flow [7].

The symptoms can be difficult to identify in utero, especially as suggestive signs such as bloody urine are missing. Moreover, there can be technical obstacles (unfavorable position of the fetus, multiple pregnancies, and lack of echogenicity of some patients). There is also the possibility of false positives or spontaneous recovery. A prenatal ultrasound diagnosis can be suggested in cases of a large hyperechoic kidney, hyperechogenicity following the path of the interlobular veins, thrombus in the inferior vena cava, and Doppler indexes in the renal artery with
reverse flow. There is a prognostic relation between kidney size and postnatal consequences: the larger the kidney, the worse the prognosis [8]. Patients with a family or personal history of thrombosis, thrombophilia or autoimmune disease, diabetes, fetal growth restriction or hydropsy should be subjected to additional ultrasounds. In these patients in particular, an extra focus on kidney examination is recommended. Medical management of renal vein thrombosis includes aggressive hydration and anti-coagulation. Nevertheless, previous studies report conflicting data regarding the benefit of anticoagulation with regard to long-term renal function, particularly in cases of bilateral renal vein thrombosis [3]. Thrombolytic therapy may be considered in cases of bilateral renal vein thrombosis, especially if there is concomitant renal failure [9]. Definitive surgical treatment consists of nephrectomy and thrombectomy on a non-urgent basis, provided there is no caval extension and obstruction. Thrombectomy for bilateral renal vein thrombosis with caval involvement and obstruction has been described once before, but with subsequent unilateral nephrectomy [10]. Recently, Lee et al. [4] showed that bilateral renal vein thrombosis can be successfully managed with early surgical thrombectomy without the need for nephrectomy, thereby avoiding the significant morbidity associated with infant dialysis and renal transplantation. Successful restoration of renal function after surgical thrombectomy in his patient illustrates an encouraging treatment option. However, the relatively small number of reported cases and lack of prospective trials have opened up debate regarding the best way to manage this condition [11].

CONCLUSION

To date, there are still many unresolved issues regarding antenatal vein thrombosis. Diagnostic possibilities and prognostic probabilities still show large discrepancies. It would be ideal to hold a register on a large scale, to collect different cases of reported antenatal renal vein thrombosis, from different obstetric teams. A standardized approach for monitoring, surveillance and prevention for subsequent pregnancies is yet to be defined. It is essential to learn to diagnose it, as is it
necessary to update obstetric ultrasound books and teaching methods for obstetricians.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES
1. Bokenkamp A, von Kries R, Nowak-Gott U, and al. Neonatal renal venous thrombosis in Germany between 1992 and 1994: epidemiology, treatment and outcome. Eur J Pediatr 2000; 159: 44–48
2. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. Pediatrics 1995; 96: 939–943
3. Lau KK, Stoffman JM, Williams S, Mc Cusker P, Brandao L, Patel S. Neonatal renal vein thrombosis: review of the English-language literature between 1992 and 2006; Pediatrics 2007: 1278–1284.
4. Leela S, Ananthb P, Boyd T, Esrickb E. Successful surgical thrombectomy for neonatal IVC and bilateral renal vein thrombosis. Journal of Pediatric Surgery Case Reports 2014; 2 : 176–179
5. Kuhle 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. ThrombHaemost 2004; 92: 729–733
6. Dahms BB, Boyd T, Redline RW. Severe perinatal liver disease associated with fetal thrombotic vasculopathy. Pediatr Dev Pathol 2002; 5: 80–85
7. Kraft JK, Brandão LR, Navarro OM. Sonography of renal venous thrombosis in neonates and infants: can we predict outcome? PediatrRadiol 2010; 41: 299–307
8. Winyard PJ, Bharucha T, De Bruyn R, and al. Perinatal renal venous thrombosis: presenting renal length predicts outcome. Arch Dis Child Fetal Neonatal 2006; 91: 273-278
9. V. JaakoDardashti V, Békássy ZD, Ljung R, JGelberg J, Wingren P, Simonsen O. Successful thrombolysis of neonatal bilateral renal vein thrombosis originating in the IVC. PediatrNephrol 2009; 24: 2069–2071
10. Clark AG, Saunders A, Bewick M, Haycock G, Chantler C. Neonatal inferior vena cava and renal venous thrombosis treated by thrombectomy and nephrectomy. Arch Dis Child 1985; 60: 1076–1077.

11. Moaddab A, Shamshirsaz AA, Ruano R, Salmanian B, Lee W, Belfort MA, Espinoza J. Prenatal Diagnosis of Renal Vein Thrombosis: A Case Report and Literature Review. Fetal Diagn Ther 2015; 10: 42-45

FIGURE LEGENDS

Figure 1: 1rst twin’s kidneys. The right kidney appears smaller and hyperechoic. The left kidney measured 49 mm (>90th percentile), the right kidney 39mm.

Figure 2: Macroscopic examination of the fetal kidneys recovering hemorrhagic infarction with renal vein thrombosis extended to the inferior vena cava. (H: Hematoma; R: Kidney; S: Adrenal gland).

Figure 3: Medullar hemorrhagic infarction of the kidney.

Figure 4: Renal hemorrhagic infarction of the cortex.

Figure 5: Recent thrombosis of the renal vein. The presence of calcifications confirms that the thrombosis was ante mortem.

FIGURES

Figure 1: 1rst twin’s kidneys. The right kidney appears smaller and hyperechoic. The left kidney measured 49 mm (>90th percentile), the right kidney 39mm.
Figure 2: Macroscopic examination of the fetal kidneys recovering hemorrhagic infarction with renal vein thrombosis extended to the inferior vena cava. (H: Hematoma; R: Kidney; S: Adrenal gland).

Figure 3: Medullar hemorrhagic infarction of the kidney.
Figure 4: Renal hemorrhagic infarction of the cortex.

Figure 5: Recent thrombosis of the renal vein. The presence of calcifications confirms that the thrombosis was ante mortem.