Management of uncommon disorders in pregnancy: Von Hippel–Lindau disease, Gitelman syndrome, and Nutcracker syndrome

Basma Merhi¹, Margaret Miller², Aviya Lanis³, Brittany Katz³, Tiffany Hsu³ and Iris Tong⁴

Abstract

Uncommon renal disorders in pregnancy can be challenging to manage given limited evidence in the literature to guide management. We present a series of three uncommon renal disorders in pregnancy: Von Hippel–Lindau disease, Gitelman syndrome, and Nutcracker syndrome. Previously published case reports with differing outcomes offer some guidance to the management of these disorders in pregnancy. In this case series, we address the management of these syndromes during pregnancy and discuss the maternal and fetal outcomes. All three of our patients had good maternal and fetal outcomes, which will contribute to current data on maternal and fetal outcomes in these rare diseases, which is limited.

Keywords

Pregnancy, Von Hippel–Lindau disease, Gitelman syndrome, Nutcracker syndrome

Date received: 8 June 2016; accepted: 9 November 2016

Introduction

The care of pregnant women with renal disorders must be provided vigilantly by a multidisciplinary team to avoid potentially dangerous and preventable clinical consequences to the mother and fetus. Although patients may initially be asymptomatic, renal disorders may worsen during pregnancy and postpartum. Here, we present a series of three uncommon renal disorders in pregnancy: Von Hippel–Lindau disease (VHL), Gitelman syndrome (GS), and Nutcracker syndrome (NS). Informed consent was obtained verbally from each patient to be included in this case series. Little information in the literature exists regarding the management of these disorders during pregnancy; case reports with differing outcomes have been published. We will address the management of these syndromes during pregnancy as well as discuss the maternal and fetal outcomes. These cases are important addition to the literature as data on maternal and fetal outcomes in these rare disorders are limited; additional research is needed as the current literature on the management of these disorders is also limited.

Case 1

A 30-year-old woman G4P1A2T0 with VHL disease diagnosed at age 12 presented to our obstetric medicine clinic at 22-week gestation. She had a history of pheochromocytoma, multiple renal cell carcinomas (RCCs), and a retinal tumor, which were all successfully resected; her pheochromocytoma was resected six years prior to presentation. After her first pregnancy two years prior, the patient was lost to follow-up and did not continue annual screenings for VHL. She denied symptoms; vital signs and physical examination were normal. Her blood pressure remained normal throughout pregnancy. She declined prenatal genetic testing. Eye exam, serum metanephrine levels, and magnetic resonance imaging (MRI) of the brain were normal. MRI of the spine revealed no spinal lesions but demonstrated bilateral renal masses. Urinalysis was negative. As gadolinium is typically avoided in pregnant patients, urology recommended further evaluation with renal ultrasound (US) rather than MRI without gadolinium. Renal US revealed multiple renal cysts and bilateral solid masses—a 2.9 cm

mass in the right lower pole, a 2.3 cm mass in the left upper pole, and a 1.6 cm mass in the left upper pole—which were highly suspicious for RCC. Renal vein Doppler was not performed. Her prior abdominal MRI with gadolinium in 2012 revealed a 1.6 cm mass in the right upper pole, a 2.4 cm mass in the right lower pole, a 1.4 cm mass in the posterior right kidney, and a 1.6 cm mass in the left upper pole, which were stable from 2008. Given the discrepant results compared to the prior MRI, oncology evaluated the patient and deferred an abdominal MRI with gadolinium until postpartum as RCCs in VHL are typically slow growing.¹ The patient delivered a healthy 6 lb 8 oz (2948 g) girl at 40-week gestation by cesarean section secondary to fetal intolerance to labor. The patient was started on the contraceptive vaginal ring. Three months postpartum, abdominal MRI with gadolinium revealed a 2.4 cm renal mass in the lower pole of the right kidney (Figure 1(a)) and a 1.8 cm renal mass in the upper pole of the left kidney (Figure 1(b)). The patient was then referred for follow-up with her oncologist and for consultation with a surgeon for further evaluation.

Case 2

A 33-year-old G2P1 patient with GS presented to our clinic at 10-week gestation. After a successful pregnancy without complications 13 years

¹Division of Nephrology, Department of Medicine, Alpert Medical School of Brown University, Providence, USA

²Division of Obstetric Medicine, Department of Medicine, Alpert Medical School of Brown University, Providence, USA

³Internal Medicine Residency Program, Santa Clara Valley Medical Centre, California, USA

⁴Division of General Internal Medicine, Department of Medicine, Alpert Medical School of Brown University, Providence, USA

Corresponding author:

Basma Merhi, Department of Medicine, Alpert Medical School of Brown University, 593 Eddy St, APC 9, Providence, RI 02903, USA.

Email: bmerhi@lifespan.org

Figure 1. MRI of abdomen revealed a 2.4 cm solid renal mass in the lower pole of the right kidney (a) and a 1.8 cm solid renal mass in the upper pole of the left kidney (b). MRI: magnetic resonance imaging.

prior, she experienced an eight-year history of muscle cramps, palpitations, and intermittent hypokalemia that responded to oral potassium and magnesium supplementation. Her diagnosis of GS was made clinically; she did not undergo genetic testing due to cost. She denied muscle cramps, fatigue, polyuria, nocturia, or joint pain. Her medications were amiloride 10 mg daily, magnesium oxide 1500 mg daily, and potassium chloride 160 mEq daily. Her vital signs and physical examination were normal. Potassium was 3.6 mEq/l and magnesium was 1.3 mEq/l. The patient was not compliant with the timing of laboratory testing and follow-up appointments. Throughout her pregnancy, she did complete laboratory testing every approximately 6–8 weeks. Her potassium level ranged from 3.4 to 3.7 mEq/dl (normal range 3.6–5.1 mEq/dl) and her magnesium level ranged from 0.9 to 1.3 mEq/dl (normal range 1.3–1.9 mEq/dl). Urinary levels were not obtained. Her bicarbonate level ranged from 23 to 26 mEq/dl (normal range 22–32 mEq/dl). She required no change in dosage of her amiloride or potassium chloride during pregnancy or labor as her potassium levels remained relatively stable. To our knowledge, the patient did not modify her dietary intake of potassium. If the patient were not compliant with potassium supplementation at the beginning of her pregnancy and became compliant during her pregnancy, this could explain the lack of increased potassium requirements, which is typically expected in pregnancy. Her magnesium oxide dosage was increased but it was unclear if the patient was compliant with her magnesium supplements as her magnesium level remained low and she was noncompliant with follow-up visits to our clinic. One week prior to her due date, she was induced by artificial rupture of membranes secondary to gestational hypertension. She delivered a healthy 7 lb 3 oz (3260 g) baby girl vaginally. Her blood pressure normalized two days after delivery.

Case 3

A 31-year-old G2P1A0T0 woman with NS, diagnosed five months prior, presented to our clinic at 13-week gestation. She denied flank pain; her blood pressure and kidney function were normal. Two months prior to becoming pregnant, the patient had an episode of gross hematuria. Workup at that time included a computed

Figure 2. CT of abdomen and pelvis with IV contrast demonstrating dilated left gonadal vein (a) and dilated parametrial vessels (b). CT: computed tomography; IV: intravenous contrast.

tomography (CT) of the abdomen and pelvis with intravenous contrast which demonstrated a dilated left gonadal vein (Figure 2(a)) and dilated left parametrial vessels (Figure 2(b)) consistent with left renal vein compression and suggestive of NS. She was referred to urology for further evaluation; based on her clinical picture and CT findings, urology confirmed a diagnosis of NS. She had an uncomplicated pregnancy without further episodes of hematuria and a spontaneous vaginal delivery of a healthy 9 lb 2 oz (4139 g) boy at 40-week gestation.

Discussion

VHL disease is a rare autosomal dominant, neoplastic disorder, which typically presents in young adulthood with a variety of benign and malignant tumors.^{2,3} The incidence of VHL is one in 36,000 persons. The most common tumors involve the central nervous system (CNS) (brain, spine, retina, and middle ear) and viscera (pancreas, kidney, adrenal, epididymis, and broad ligament).^{2,3} The majority of pregnant women with VHL have a favorable outcome with high fetal survival (96.4%) and low maternal morbidity (5.4%),⁴ but concerns in pregnancy include CNS hemangioblastomas, which can cause increased intracranial pressure and complications with neuraxial anesthesia, and pheochromocytoma, which can mimic preeclampsia with grave consequences to the mother and fetus.⁵ It is unclear whether pregnancy induces the growth and progression of tumors associated with VHL.^{6,7} A study by Frantzen et al.⁶ demonstrated that pregnancy induces cerebellar hemangioblastoma progression in patients with VHL disease and leads a high pregnancy complication rate (17%) while two other studies demonstrated that pregnancy was not associated with growth

or hemangioblastomas^{7,8} or RCC.⁸ We were unable to find data on the growth of pheochromocytoma associated with VHL in pregnancy.

Annual screening for all VHL patients involves regular physical and ophthalmologic exams, serum or urinary catecholamines, MRI of brain and spine, and abdominal US or CT. Surgical management of existing symptomatic tumors should be determined on an individual basis. Pheochromocytoma is a feared complication of VHL in pregnancy that can present similarly to preeclampsia with high maternal and fetal mortality. Screening is crucial as early detection and management can improve outcomes. In pregnancy, urinary catecholamines should be checked in early, mid, and late pregnancy, and noncontrast MRI of brain and spine should be checked in the fourth month of pregnancy. Surgical resection may be indicated, preferably before 24 weeks of gestation or after delivery.⁹ RCC in pregnancy is not well represented in the literature as it usually presents in later decades of life. In patients with VHL disease, nephron-sparing surgery or radiofrequency ablation can provide earlier treatment of small tumors and are associated with an improved overall renal prognosis.¹⁰ However, an individualized decision may be made to postpone surgery until after delivery, as in the case of our patient. Spinal hemangioblastomas are typically in the thoracic rather than lumbar area.¹¹ However, due to concern for tumor rupture during neuraxial anesthesia, spinal imaging by MRI is crucial. Given the risk of CNS hemangioblastoma in VHL, cesarean section may be considered to avoid the increase in cerebrospinal fluid pressure that occurs during vaginal delivery.⁹ Given a 50% risk of inheritance, genetic counseling should be offered to patients, and women should be provided preconception counseling.⁶

Described in 1966 by Gitelman et al.,¹² GS is an autosomal recessive disorder with a prevalence of one in 40,000 persons. GS is caused by a mutation in the SLC12A3 gene on chromosome 16 (16q13) which results in a loss of function of the thiazide-sensitive sodium chloride cotransporter causing hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria due to the increased volume of sodium delivered to the distal convoluted tubule.

Characteristic features include salt craving, fatigue, and orthostatic hypotension. Although GS patients are typically normotensive at rest, there is noted activation of the renin–angiotensin–aldosterone axis.¹³ Because hypomagnesemia and hypokalemia tend to worsen during pregnancy due to the expansion of the extracellular volume and increased renal clearance, the management of maternal GS can be challenging. Data are limited to case reports with the mainstay of therapy being potassium and magnesium supplementation. Talaulikar and Falt¹⁴ in 2005 reported a sixfold increase in potassium and magnesium requirements in their patient. GS has been associated with oligohydramnios and intrauterine growth restriction (IUGR), as well as significant maternal morbidity due to electrolyte imbalances.^{13,15} Basu et al.¹⁵ reported that normalization of potassium and magnesium levels is not required for a good obstetric and neonatal outcome, but due to the expected physiologic demands of labor and delivery, careful monitoring and replacement of electrolytes during the course of labor is prudent. Although spironolactone has been associated with feminization of male fetuses in rat studies,¹⁶ its use in a pregnant patient with GS has been reported.¹⁷ Amiloride, eplerenone, or indomethacin increase potassium concentrations in patients with GS¹⁸; amiloride has been used in a case report to treat hypokalemia during pregnancy with successful outcome.¹⁹

Of the 24 reported pregnancies in 18 women with GS,^{14,15,17,20–24} 20 had fetal complications. Six pregnancies were complicated by oligohydramnios, one was complicated by IUGR, and one resulted in fetal demise at 28-week gestation in the setting of poorly controlled electrolyte levels, although multiple other cases have reported successful pregnancy without sustained normalization of electrolyte levels.^{17,25,26}

NS results from the compression of the left renal vein (LRV) by the aorta and superior mesenteric artery (SMA), which can lead to venous hypertension, development of intra- and extra-renal collaterals, and gonadal vein reflux.²⁷ While patients with NS are often asymptomatic, some may experience hematuria, flank pain, varicocele, orthostatic proteinuria, and orthostatic intolerance. The prevalence of NS is

unknown but may be slightly higher in females.²⁸ NS is not hereditary, and low body mass index may predispose patients to development of the syndrome.²⁹

US, CT, and MRI are used to diagnose NS with US being the preferred tool.^{28,30} Management ranges from observation to nephrectomy, based on symptom severity. Acetylsalicylic acid may reduce fatigue, pain, and hematuria in NS. Surgery is reserved for patients with severe symptoms and includes stenting of the LRV, ligation of collateral veins, LRV or SMA vascular transpositions, and renal autotransplantation.^{28,31}

Although NS is generally benign and associated with a very good prognosis, physiological changes in pregnancy may cause a widening of the diameter of the aorta that further compresses the LRV.³² Pregnant patients typically present with hematuria, pelvic congestion syndrome, or vulvar varicosities^{33,34}; NS should be in the differential diagnosis of postpartum patients with hematuria. Management does not differ in pregnancy, but there is limited evidence-based literature on the management of NS in pregnancy. However, pregnant women who received stent placement should receive anticoagulation to prevent thrombosis.³⁵

In conclusion, providers should be aware of the common concerns of these uncommon disorders during pregnancy. Concerns in VHL disease during pregnancy include adequate screening, potential tumor progression, and development of pheochromocytoma, as well as complications with anesthesia and delivery. Encouragingly, VHL in pregnancy is associated with a high fetal survival rate and low maternity morbidity. GS in pregnancy, if managed with electrolyte supplementation and proper surveillance for oligohydramnios and IUGR, is likely to have a favorable outcome. Maternal symptoms may worsen during the pregnancy, requiring increased supplementation and comprehensive peripartum observation. There is little evidence of fetal risk in previously reported cases. Additional research is needed to better understand the impact of NS in pregnancy, along with appropriate treatment plans to avoid complications. Proper surveillance, vigilant management, and appropriate treatment plans and mode of delivery will likely effect favorable maternal and fetal outcomes in pregnant women with these rare renal disorders. Again, additional research is needed, as current literature on the management is limited to case reports.

Acknowledgements

Cases from this study were presented at the North American Society of Obstetric Medicine Annual Meeting, Banff, Alberta, Canada, 14–15 November 2015.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

The authors confirm that verbal consent from each patient was obtained and documented.

Guarantor

BM

Contributorship

All authors contributed to, reviewed, and edited the manuscript and approved the final version.

References

- Jilg CA, Neumann HP, Glasker S, et al. Growth kinetics in von Hippel-Lindau-associated renal cell carcinoma. *Urol Int* 2012; 88: 71–78.
- Lamiell JM, Salazar FG and Hsia YE. von Hippel-Lindau disease affecting 43 members of a single kindred. *Medicine (Baltimore)* 1989; 68: 1–29.
- Zbar B, Kaelin W, Maher E, et al. Third international meeting on von Hippel-Lindau disease. *Cancer Res* 1999; 59: 2251–2253.
- Grimbert P, Chauveau D, Remy SR, et al. Pregnancy in von Hippel-Lindau disease. *Am J Obstet Gynecol* 1999; 180: 110–111.
- Lenders JW. Pheochromocytoma and pregnancy: a deceptive connection. *Eur J Endocrinol* 2012; 166: 143–150.
- Frantzen C, Kruizinga RC, van Asselt SJ, et al. Pregnancy-related hemangioblastoma progression and complications in von Hippel-Lindau disease. *Neurology* 2012; 79: 793–796.
- Ye DY, Bakhtian KD, Asthagiri AR, et al. Effect of pregnancy on hemangioblastoma development and progression in von Hippel-Lindau disease. *J Neurosurg* 2012; 117: 818–824.
- Binderup ML, Budtz-Jorgensen E and Bisgaard ML. New von Hippel-Lindau manifestations develop at the same or decreased rates in pregnancy. *Neurology* 2015; 85: 1500–1503.
- Adekola H, Soto E, Lam J, et al. von Hippel-Lindau disease and pregnancy: what an obstetrician should know. *Obstet Gynecol Surv* 2013; 68: 655–662.
- Joly D, Mejean A, Correas JM, et al. Progress in nephron sparing therapy for renal cell carcinoma and von Hippel-Lindau disease. *J Urol* 2011; 185: 2056–2060.
- Banerjee T and Hunt WE. A case of spinal cord hemangioblastoma and review of the literature. *Am Surg* 1972; 38: 460–464.
- Gitelman HJ, Graham JB and Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. *Trans Assoc Am Physicians* 1966; 79: 221–235.
- Naesens M, Steels P, Verberckmoes R, et al. Bartter's and Gitelman's syndromes: from gene to clinic. *Nephron Physiol* 2004; 96: 65–78.
- Talaulikar GS and Falk MC. Outcome of pregnancy in a patient with Gitelman syndrome: a case report. *Nephron Physiol* 2005; 101: 35–38.
- Basu A, Dillon RD, Taylor R, et al. Is normalisation of serum potassium and magnesium always necessary in Gitelman Syndrome for a successful obstetric outcome? *BJOG* 2004; 111: 630–634.
- Hecker A, Hasan SH and Neumann F. Disturbances in sexual differentiation of rat fetuses following spironolactone treatment. *Acta Endocrinol (Copenh)* 1980; 95: 540–545.
- Daskalakis G, Marinopoulos S, Mousiolis A, et al. Gitelman syndrome-associated severe hypokalemia and hypomagnesemia: case report and review of the literature. *J Matern Fetal Neonatal Med* 2010; 23: 1301–1304.
- Blanchard A, Vargas-Poussou R, Vallet M, et al. Indomethacin, amiloride, or eplerenone for treating hypokalemia in Gitelman syndrome. *J Am Soc Nephrol* 2015; 26: 468–475.
- Mathen S, Venning M and Gillham J. Outpatient management of Gitelman's syndrome in pregnancy. *BMJ Case Rep* 2013. doi:10.1136/bcr-2012-007927.
- Jones JM and Dorrell S. Outcome of two pregnancies in a patient with Gitelman's syndrome—a case report. *J Matern Fetal Investig* 1998; 8: 147–148.
- de Haan J, Geers T and Berghout A. Gitelman syndrome in pregnancy. *Int J Gynaecol Obstet* 2008; 103: 69–71.
- McCarthy FP, Magee CN, Plant WD, et al. Gitelman's syndrome in pregnancy: case report and review of the literature. *Nephrol Dial Transplant* 2010; 25: 1338–1340.
- de Arriba G, Sanchez-Heras M and Basterrechea MA. Gitelman syndrome during pregnancy: a therapeutic challenge. *Arch Gynecol Obstet* 2009; 280: 807–809.
- Lakhi N, Jones J and Govind A. Fetal demise despite normalisation of serum potassium in Gitelman syndrome. Case report and literature review. *Aust N Z J Obstet Gynaecol* 2010; 50: 301–302.
- Rusavy Z, Hudec A, Karbanova J, et al. [Gitelman syndrome in pregnancy—a severe hypokalemia with favorable perinatal prognosis]. *Ceska Gynekol* 2012; 77: 421–423.
- Moustakakis MN and Bockorny M. Gitelman syndrome and pregnancy. *Clin Kidney J* 2012; 5: 552–555.
- Singh R, Griffiths A and Trivedi A. Nutcracker syndrome in pregnancy: a tough nut to crack? *Aust N Z J Obstet Gynaecol* 2008; 48: 119–120.
- Kurklinsky AK and Rooke TW. Nutcracker phenomenon and nutcracker syndrome. *Mayo Clin Proc* 2010; 85: 552–559.
- Ozkurt H, Cenker MM, Bas N, et al. Measurement of the distance and angle between the aorta and superior mesenteric artery: normal values in different BMI categories. *Surg Radiol Anat* 2007; 29: 595–599.
- Shaper KR, Jackson JE and Williams G. The nutcracker syndrome: an uncommon cause of haematuria. *Br J Urol* 1994; 74: 144–146.
- Hohenfellner M, Steinbach F, Schultz-Lampel D, et al. The nutcracker syndrome: new aspects of pathophysiology, diagnosis and treatment. *J Urol* 1991; 146: 685–688.
- Rudloff U, Holmes RJ, Prem JT, et al. Mesoaortic compression of the left renal vein (nutcracker syndrome): case reports and review of the literature. *Ann Vasc Surg* 2006; 20: 120–129.
- Scultetus AH, Villavicencio JL and Gillespie DL. The nutcracker syndrome: its role in the pelvic venous disorders. *J Vasc Surg* 2001; 34: 812–819.
- Gopalakrishnan G, al-Awadi K, Bhatia V, et al. Renal arteriovenous malformation presenting as haematuria in pregnancy. *Br J Urol* 1995; 75: 110–111.
- Itoh S, Yoshida K, Nakamura Y, et al. Aggravation of the nutcracker syndrome during pregnancy. *Obstet Gynecol* 1997; 90: 661–663.