Kidney Medicine

Urinary Oxalate Excretion During Pregnancy in Primary Hyperoxaluria Type 1: A Report of 4 Cases

Jing Miao, Ramila A. Mehta, Andrea Kattah, Suzanne M. Norby, John C. Lieske, and Dawn S. Milliner

Primary hyperoxaluria (PH) is a rare genetic disorder characterized by excessive oxalate production because of specific gene defects. PH1 is the most prevalent type, causing recurrent kidney stone disease and often leading to chronic kidney disease and kidney failure. Our previous study suggested that pregnancy did not adversely affect kidney function in female patients with PH. In this study, we identified 4 PH1 cases with urinary oxalate (UOx) measurements during pregnancy from the Rare Kidney Stone Consortium and Oxalosis and Hyperoxaluria Foundation PH registry to investigate UOx levels during pregnancy in patients with PH1. The PH Registry is approved by the Institutional Review Board of Mayo Clinic (Rochester, MN). All 4 showed a decrease in UOx during pregnancy when compared with before pregnancy and after delivery. These findings contrast with those of the general population, in which the UOx tends to increase during pregnancy because of a simultaneous physiological increase in the glomerular filtration rate. Elucidating the mechanism underlying reduced UOx during pregnancy in PH1 could suggest novel PH therapies. These findings could also affect the clinical management and have implications regarding the safety of withholding novel PH1-directed molecular therapies that currently have uncertain safety profiles during pregnancy. We highlight the need for additional data on urinary changes in patients with PH and other populations while pregnant to clarify changes in UOx throughout pregnancy.

Complete author and article information provided before references.

Correspondence to D.S. Milliner (Milliner.Dawn@mayo.edu)

Kidney Med. 6(6):100824. Published online April 16, 2024.

doi: 10.1016/j.xkme.2024.100824

INTRODUCTION

Primary hyperoxaluria (PH) is a rare genetic disorder affecting the metabolism of glyoxylate. There are 3 types of PH, each associated with a specific gene defect as a result of excessive oxalate production. As the most prevalent type, PH1 accounts for 70%-80% of all cases.[1] PH1 is caused by pathogenic changes in the *AGXT* gene that encodes alanine-to-glyoxylate aminotransferase (AGT), an enzyme mainly expressed in the liver in which it plays a crucial role in glyoxylate degradation through a pyridoxal-5-phosphate dependent pathway.[2] The resulting increase in generation of oxalate leads to hyperoxaluria, ongoing calcium oxalate crystal deposition within the kidneys, and recurrent urinary stone disease. Chronic kidney disease (CKD) and kidney failure often ensue,[1,2] although it is hoped that with newer disease-modifying therapies now available[3] or under development,[4] kidney outcomes will improve in the future.

Our previous study reported that pregnancy did not appear to negatively affect kidney function in a cohort of female patients with PH,[5] despite concerns regarding potential volume contraction because of emesis in early pregnancy, stone complications, and risks to kidney function related to preeclampsia or obstetric complications at delivery. However, the influence of pregnancy itself on urinary oxalate excretion in women with PH remains undetermined. In this study, we performed a thorough examination of the Rare Kidney Stone Consortium (RKSC) and Oxalosis and Hyperoxaluria Foundation (OHF) PH registry[5] to identify all cases with 24-hour urinary oxalate measurements (UOx) before, during, and after pregnancy.

CASE REPORT

A total of 4 PH1 cases with UOx data available during pregnancy were identified from the RKSC and OHF Registry (Table 1). Cases 1 and 2 received a consistent pharmacologic dose of vitamin B6 (5-10 mg/kg) throughout the prepregnancy, pregnancy, and postdelivery periods. Cases 3 and 4 each received a short course of vitamin B6 before pregnancy but did not take it during pregnancy or after delivery. Urinary stone prevention routines were not changed during pregnancy in any of the cases. None received any disease-modifying PH medications during pregnancy (specifically siRNA treatments).

All 4 cases demonstrated a significant decrease in UOx during pregnancy compared with the time of diagnosis, and closest to the beginning of gestation and outside of gestation (Fig 1). Case 1 had 6 UOx measurements during pregnancy with an average (0.50 ± 0.20 mmol/24 h/1.73 m^2) significantly lower when compared with before pregnancy (2.06 ± 0.55 mmol/24 h/1.73 m^2, based on 4 measurements) and after delivery (1.09 ± 0.45 mmol/24 h/1.73 m^2, based on 11 measurements) (Fig 2).

Estimated glomerular filtration rates (eGFRs) were calculated using the full-age spectrum equation.[6] In case 1, the eGFR was 40 ± 2.3 mL/min/1.73 m^2 (3 measurements) during pregnancy, which was slightly higher than the prepregnancy value of 38 mL/min/1.73 m^2. Case 4 had an eGFR of 99 and 121 mL/min/1.73 m^2 during pregnancy, higher than both prepregnancy and postdelivery values of 96 mL/min/1.73 m^2 (Fig 3).

In comparison to the phases before and after pregnancy, there was a noticeable increase in 24-hour urine calcium

Table 1. Clinical characteristics and urinary oxalate excretion change during pregnancy in 4 patients with PH1[a]

	Case 1	Case 2	Case 3	Case 4
Age at symptoms onset (y)	8	9	4	1
Age at diagnosis (y)[b]	10	30	<5	<5
PH type	PH1	PH1	PH1	PH1
AGXT genotype	c.508G>A (p.Gly170Arg) and c.33dup (p.Lys12Glnfs*156)	c.33dup (p.Lys12Glnfs*156) and c.454T>A (p.Phe152Ile)	c.1072_1179del (p.Val358fs) and c.846+1G>T (p.Gln282?)	c.508G>A (p.Gly170Arg) and c.346G>A (p.Gly116Arg)
Nephrocalcinosis, Yes/No	No	No	No	No
Systemic oxalosis, Yes/No	No	No	No	No
Treatment with vitamin B6 during pregnancy, Yes/No[c]	Yes	Yes	No	No
Pregnancy after diagnosis (y)	31	1[d]	23	32
Complications during pregnancy	Bilateral kidney stones	Hematuria	Kidney stone	UTI
Additional medications for PH in pregnancy[e]	Bicitra	No	No	No
Gestational age at delivery (wk)	40	39	40	40
Birth weight of infant (kg)	3.74	3.27	3.97	3.86
UOx excretion (mmol/24 h/1.73 m^2)				
At PH diagnosis	2.15	1.59	2.39	2.50
Before pregnancy[f]	2.06 ± 0.55 (n = 4)	1.45	1.51 ± 0.75 (n = 27)	1.06 ± 0.78 (n = 12)
During pregnancy[f]	0.54, 0.29, 0.27, 0.68, 0.44, 0.77 (0.50 ± 0.20, n = 6)	0.68	0.47, 0.38	0.40, 0.40
Post delivery[f]	1.09 ± 0.45 (n = 11)	1.72 ± 0.66 (n = 13)	1.71	0.89, 1.48
FAS-eGFR[g]				
At diagnosis	67	NA	53	NA
Before pregnancy	38	83	77	96
During pregnancy	40 ± 2.3 (n = 3)	NA	NA	99, 121
After delivery	41	95	75	96
Kidney failure, Yes/No[h]	Yes	No	No	No
Follow-up duration after pregnancy (y)	15.8	9.4	0.9	1.9

Abbreviations: PH, primary hyperoxaluria; *AGXT*, the gene of enzyme alanine-to-glyoxylate aminotransferase (AGT); UOx, urine oxalate; FAS-eGFR, estimated glomerular filtration rate calculated by full-age spectrum equation; UTI, urinary tract infection; NA, not available.

[a]In case 1, there were 2 pregnancies, though the first was lost to miscarriage at 8 weeks. Case 2 also had 2 pregnancies. There are no UOx data from the first pregnancy in either case. Cases 3 and 4 each experienced a single pregnancy. All pregnancies reported here resulted in the birth of healthy infants.

[b]Approximate ages are used for deidentification of the participants.

[c]The detail about vitamin B6 treatment including the dosage before pregnancy and after delivery is shown in Fig 1.

[d]PH in case 2 was diagnosed 1.2 years after pregnancy.

[e]Additional medications taken for PH during pregnancy, especially different from before pregnancy and after delivery.

[f]In cases for which there were 2 measurements, both are provided. When multiple measurements were available (n ≥ 3), individual values are included in addition to the mean ± standard deviation and the number of measurements (n) are reported.

[g]The eGFR was calculated using full-age spectrum equation. The values closest to beginning of pregnancy and after delivery are reported: 5.5 months before pregnancy and 4.4 months after delivery in case 1, 7 years before pregnancy and 2 years after delivery in case 2, 3 months before pregnancy and 1 month after delivery in case 3, and 4.6 months before pregnancy and 3.4 months after delivery in case 4.

[h]In case 1, kidney failure occurred 6 years after pregnancy, and kidney transplantation was performed 1 year later. The remaining cases have maintained kidney function since delivery.

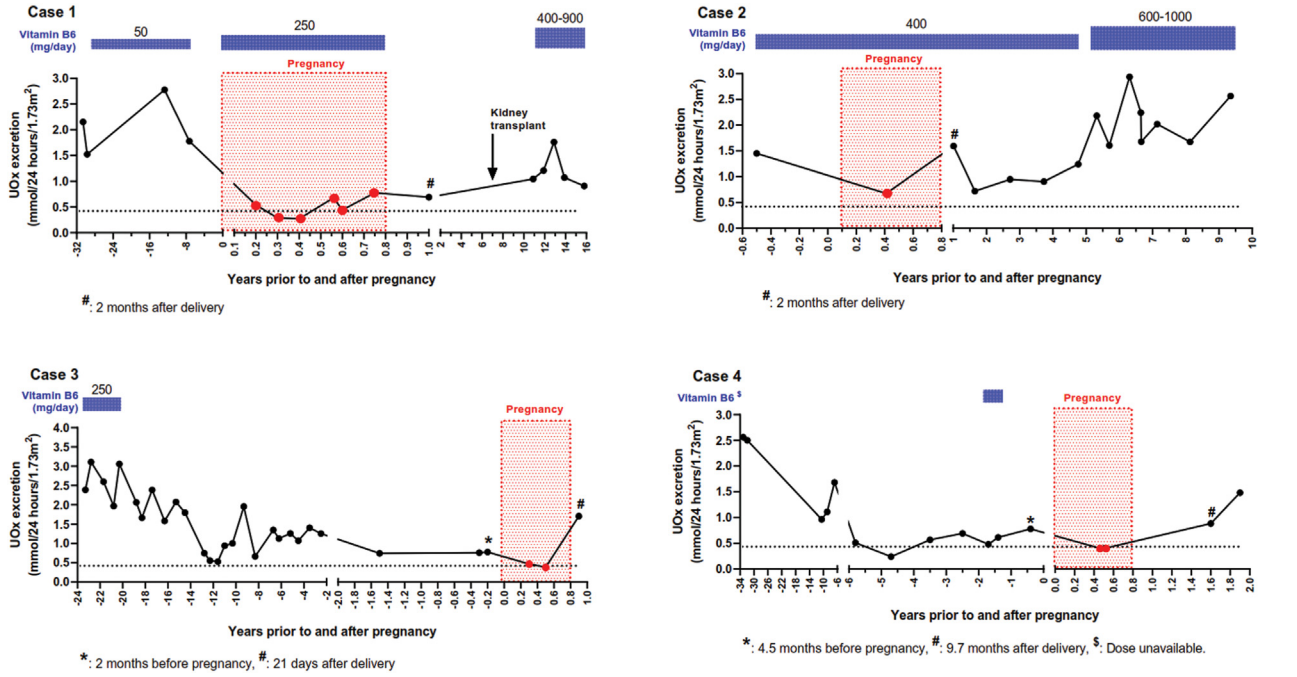
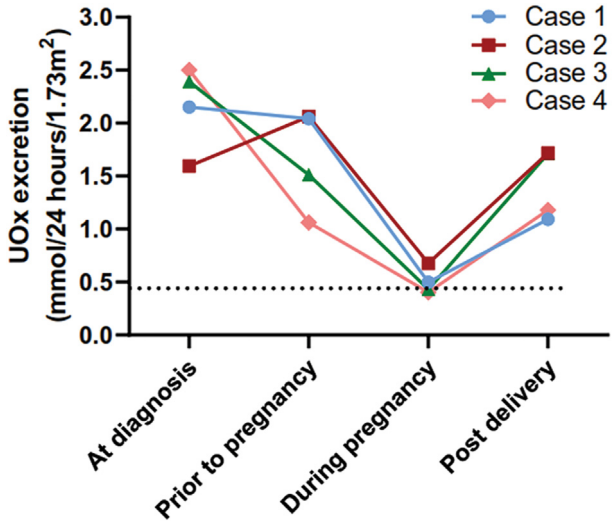


Figure 1. Urinary oxalate excretion at time points available in each patient with primary hyperoxaluria1. The origin point of the x axis is the start of pregnancy. The dashed line indicates the normal range of urinary oxalate < 0.46 mmol/24 h/1.73 m^2.



No. of measurements

	Prior	During	Post
Case 1	4	6	11
Case 2	1	1	13
Case 3	27	2	1
Case 4	12	2	2

Figure 2. Reduced urinary oxalate excretion in 4 patients with primary hyperoxaluria1 during pregnancy. For cases with multiple urinary oxalate (UOx) measurements available before, during, and after pregnancy, the mean UOx value was used for the plot. The number of measurements for each case is indicated below the graph. The dashed line indicates the normal range of UOx < 0.46 mmol/24 h/1.73 m^2.

and citrate levels during pregnancy in cases 2 and 3 (Table S1).

DISCUSSION

Women with PH1 are at risk throughout their lives for recurring stone events and for progressive loss of kidney function.[1] Pregnancy in healthy women is associated with an increased risk of symptomatic kidney stones[7] and risks of kidney compromise because of hyperemesis gravidarum, eclampsia, and other complications, including blood loss. Out of concern for the heightened risks associated with gestation, women with PH1 may be advised to avoid pregnancy or personally reluctant to become pregnant. However, little is known of UOx excretion during pregnancy in women with PH1.

In this study, we identified 4 patients with PH1 with UOx measurements available while pregnant and nonpregnant, thereby allowing for intra-individual comparisons. Surprisingly, each of the cases had a reduction in UOx during pregnancy, particularly illustrated in case 1, who had multiple UOx measurements available during pregnancy. A similar decline in UOx had been previously reported several decades ago in a single patient with PH1, who became pregnant after a successful kidney transplant, suggesting that the pregnancy may have temporarily reduced the rate of oxalate synthesis.[8] However, the interpretation of UOx values in this patient was complicated by the absence of UOx values before CKD stage 5 and the timing of kidney failure and dialysis just 1 year before the onset of pregnancy.

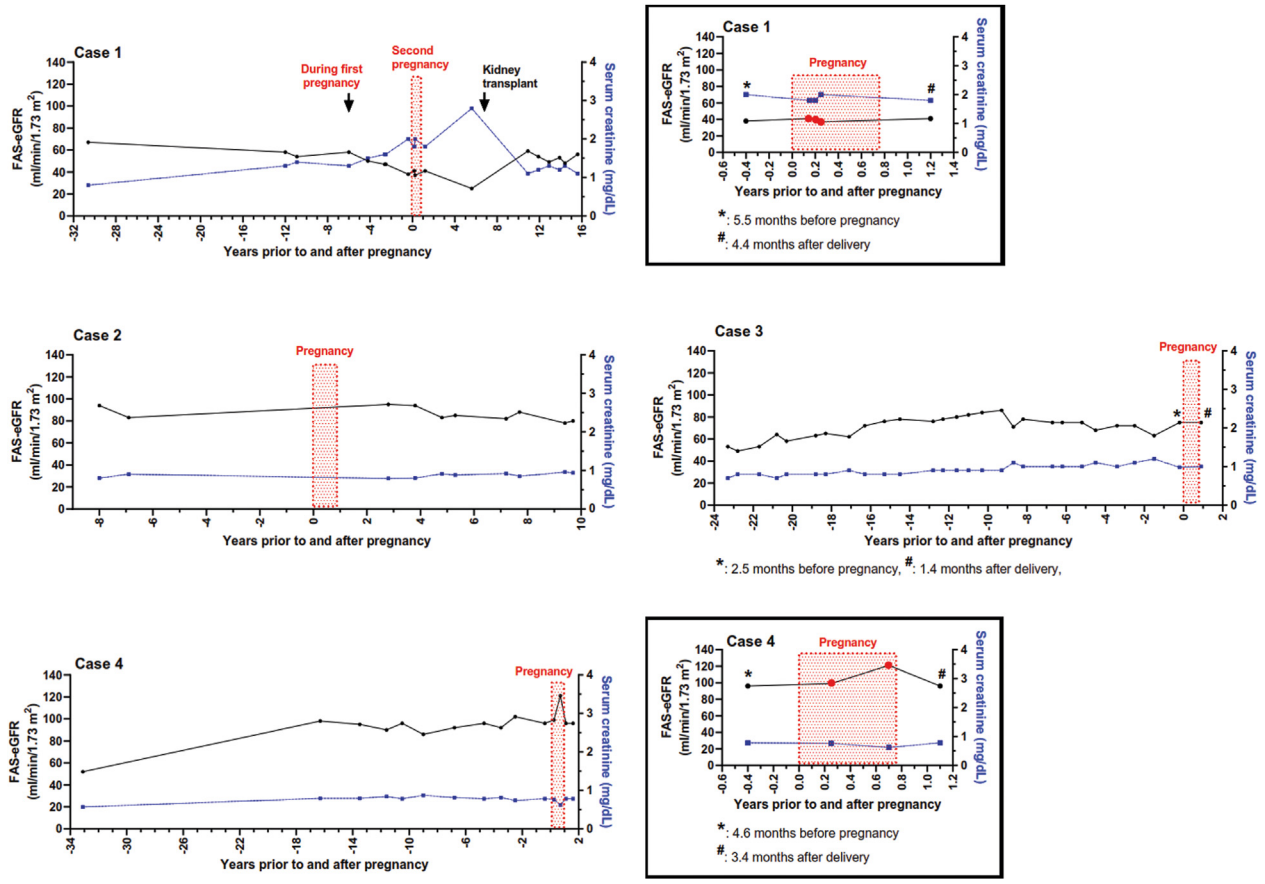


Figure 3. Estimated glomerular filtration rate and serum creatinine at time points available in each patient with primary hyperoxaluria1. The origin point of the x axis is the start of pregnancy. The specific area throughout pregnancy for cases 1 and 4 is magnified and displayed on the right-hand side. In cases 2 and 3, estimated glomerular filtration rate and serum creatinine measurements during pregnancy are unavailable.

Increased metabolic demand during pregnancy is accompanied by a physiological increase in the GFR,[9] resulting in elevation of urinary sodium, calcium, citrate, oxalate, and uric acid excretion.[9,10] Maikranz et al[10] demonstrated in 11 healthy pregnant women that the UOx increased during the second and third trimesters when compared with the first trimester measurements in the same participants and was significantly higher than those in nonpregnant females. Smith et al[11] also reported that the UOx was higher during the third trimester of pregnancy in 17 healthy women when compared with the UOx in the same participants when not pregnant. These observations would be in keeping with the increase in GFR in healthy pregnancies and also observed in the participants. In contrast, Resim et al[12] studied 15 healthy pregnant women during each trimester of pregnancy. The UOx remained within the normal range and did not change significantly from the first through the third trimester.[12] Case 1 who experienced progressive CKD before pregnancy, eventually required a kidney transplant several years after delivery. It is interesting that the eGFR was stable during both of her pregnancies. Although possibly influenced by a decline in the eGFR of approximately 60 mL/min/1.73 m^2 at the time of her last prepregnancy measurement to 40 mL/min/1.73 m^2, the marked decline in UOx during her pregnancy appears disproportionate, thus does not appear to be because of a decrease in the eGFR.

In the absence of AGT, peroxisomal glyoxylate cannot be properly converted to glycine and instead moves to the cytosol. Once in the cytosol, it undergoes conversion into either oxalate by the enzyme lactate dehydrogenase or glycolate by the enzyme glyoxylate reductase or hydroxypyruvate reductase.[13,14] Thus, overproduction of both oxalate and glycolate occurs in PH1.[15] Over 200 different pathogenic variants in the *AGXT* gene have been described to date. These mutations can lead to various functional consequences, such as the loss of enzyme catalytic activity while retaining AGT immunoreactivity and the loss of both catalytic activity and immunoreactivity.[16] In our study, cases 1 and 4 carried a monoallelic pathogenic variant c.508G>A, whereas case 2 carried a pathogenic variant c.454T>A. Monoallelic presence of either of these 2 missense mutations results in partial vitamin B6 responsiveness with an ~30% reduction of UOx.[17] Case 3 presented 2 novel pathogenic variants with unknown effects on vitamin B6 treatment. She appeared clinically

nonresponsive to a trial of vitamin B6 in early childhood. We acknowledge that medication histories have limitations. Though serum levels of vitamin B6 were not available, cases 1, 2, and 3 had very high UOx while receiving large doses of vitamin B6 before and after pregnancy. Thus, it seems unlikely that vitamin B6 was responsible for the reduction in UOx observed during pregnancy.

The mechanism underlying the decrease in UOx observed in these patients with PH1 remains unclear. Previous, albeit limited, studies have detailed changes in hepatic amino acid metabolism during pregnancy that result in reduced urea generation.[18] Thus, it is possible that overall changes in hepatic metabolism associated with pregnancy could directly alter the activity of enzymes related to increased oxalate generation in patients with PH1, or reduce the generation of key substrates, with the net effect of reducing oxalate generation. Future studies that include measurement of plasma oxalate, oxalate metabolic pool size, and tissue oxalate accretion rates in patients with PH1 could address this hypothesis. Additionally, hormonal shifts and lactation could also affect the urinary excretion of oxalate.[19]

To the best of our understanding, this is the first report of patients with PH1 with serial data to suggest a decrease in UOx during pregnancy since an initial single case report in 1990. We also acknowledge the limitations of this report, such as the small number of cases and the lack of complete data inherent in retrospective studies. The number of UOx measurements taken during the pregnancy was small. Also, the UOx measurements can vary over time even in the absence of changes in treatment.[20] Contributing factors to the observed decrease in UOx during pregnancy remain poorly understood, and caution is appropriate in interpretation. Nevertheless, the UOx fell in all 4 cases to a similar degree, with a rebound to the range of prepregnancy values following delivery.

In summary, our study showed a decrease in UOx during pregnancy in 4 patients with PH1 with data available while nonpregnant and pregnant. It is essential to validate these findings in additional cohorts. Elucidating the underlying mechanisms could suggest novel PH therapies. These findings could also have implications regarding the safety of withholding novel PH1-directed molecular therapies that currently have uncertain safety profiles during pregnancy.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Table S1: Urine Calcium, Citrate Levels and Creatinine to Body Weight Ratio Throughout Pregnancy in Women With Primary Hyperoxaluria Type 1 (PH1)

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Jing Miao, MD, Ramila A. Mehta, MS, Andrea Kattah, MD, Suzanne M. Norby, MD, John C. Lieske, MD, and Dawn S. Milliner, MD

Authors' Affiliations: Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN (JM, AK, JCL, DSM); Division of Biostatistics, Mayo Clinic, Rochester, MN (RAM); Division of Nephrology, University of Wisconsin School of Medicine and Public Health, Madison, WI (SMN); Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN (JCL); and Division of Pediatric Nephrology, Mayo Clinic, Rochester, MN (DSM).

Address for Correspondence: Dawn S. Milliner, MD, Division of Nephrology and Hypertension and Division of Pediatric Nephrology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Email: Milliner.Dawn@mayo.edu

Support: This project was supported by U54-DK083908 from the National Institute of Diabetes and Digestive and Kidney Diseases and National Center for Advancing Translational Sciences, the Oxalosis and Hyperoxaluria Foundation (OHF), and the Mayo Foundation.

Financial Disclosure: Dr Lieske has received consulting fees paid to Mayo Foundation from Alnylam, Arbor, BioMarin, Dicerna, Synlogic, Orfan-Bridgebio, Novobiome, Federation Bio. Research Grants from Allena, Alnylam, BioMarin, OxThera, Dicerna, Synlogic. Dr Milliner has received grant funding or contracts paid to Mayo Foundation from NIDDK, OHF, Dicerna, Alnylam, and OxThera and a consulting fee from Mirum Pharmaceuticals.

Acknowledgments: We would like to thank the patients for participating in this study. Also, we would like to thank the OHF for support of the clinical research coordinators for the PH Registry, and specifically Genia Andrist for all her help. Drs JCL, DSM contributed equally to this work.

Ethical Guidelines: The PH Registry is approved by the Institutional Review Board of Mayo Clinic (Rochester, MN), and conducted in compliance with informed consent, good clinical practice guidelines, and all applicable regulatory requirements.

Patient Protections: The authors declare that they have obtained consent from the patients reported in this article for publication of the information about him/her that appears within this Case Report and any associated supplementary material.

Peer Review: Received March 25, 2023 as a submission to the expedited consideration track with 1 external peer reviewer. Direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form February 20, 2024.

REFERENCES

1. Singh P, Viehman JK, Mehta RA, et al. Clinical characterization of primary hyperoxaluria type 3 in comparison with types 1 and 2. *Nephrol Dial Transplant*. 2022;37(5):869-875. doi:10.1093/ndt/gfab027
2. Hopp K, Cogal AG, Bergstralh EJ, et al. Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. *J Am Soc Nephrol*. 2015;26(10):2559-2570. doi:10.1681/ASN.2014070698
3. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med*. 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712
4. Baum MA, Langman C, Cochat P, et al. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. *Kidney Int*. 2023;103(1):207-217. doi:10.1016/j.kint.2022.07.025
5. Miao J, Mehta RA, Norby S, et al. Comparison of clinical features of pregnant and non-pregnant females with primary hyperoxaluria. *J Nephrol*. 2022;35(6):1771-1774. doi:10.1007/s40620-022-01253-9

6. Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant*. 2016;31(5):798-806. doi:10.1093/ndt/gfv454
7. Thongprayoon C, Vaughan LE, Chewcharat A, et al. Risk of symptomatic kidney stones during and after pregnancy. *Am J Kidney Dis*. 2021;78(3):409-417. doi:10.1053/j.ajkd.2021.01.008
8. Baker LR, Tucker B, Wood RF, Gillard MG, Purkiss P, Watts RW. Successful pregnancy in a renal transplant recipient with type I primary hyperoxaluria. *Transplantation*. 1990;49(4):811-812. doi:10.1097/00007890-199004000-00031
9. Cheung KL, Lafayette RA. Renal physiology of pregnancy. *Adv Chronic Kidney Dis*. 2013;20(3):209-214. doi:10.1053/j.ackd.2013.01.012
10. Maikranz P, Holley JL, Parks JH, Lindheimer MD, Nakagawa Y, Coe FL. Gestational hypercalciuria causes pathological urine calcium oxalate supersaturations. *Kidney Int*. 1989;36(1):108-113. doi:10.1038/ki.1989.168
11. Smith CL, Kristensen C, Davis M, Abraham PA. An evaluation of the physicochemical risk for renal stone disease during pregnancy. *Clin Nephrol*. 2001;55(3):205-211.
12. Resim S, Ekerbicer HC, Kiran G, Kilinc M. Are changes in urinary parameters during pregnancy clinically significant? *Urol Res*. 2006;34(4):244-248. doi:10.1007/s00240-006-0051-7
13. Salido E, Pey AL, Rodriguez R, Lorenzo V. Primary hyperoxalurias: disorders of glyoxylate detoxification. *Biochim Biophys Acta*. 2012;1822(9):1453-1464. doi:10.1016/j.bbadis.2012.03.004
14. Mandrile G, Beck B, Acquaviva C, et al. Genetic assessment in primary hyperoxaluria: why it matters. *Pediatr Nephrol*. 2023;38(3):625-634. doi:10.1007/s00467-022-05613-2
15. Danpure CJ. Molecular and clinical heterogeneity in primary hyperoxaluria type 1. *Am J Kidney Dis*. 1991;17(4):366-369. doi:10.1016/s0272-6386(12)80624-x
16. Fargue S, Acquaviva Bourdain C. Primary hyperoxaluria type 1: pathophysiology and genetics. *Clin Kidney J*. 2022;15(Suppl 1):i4-i8. doi:10.1093/ckj/sfab217
17. Monico CG, Rossetti S, Olson JB, Milliner DS. Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. *Kidney Int*. 2005;67(5):1704-1709. doi:10.1111/j.1523-1755.2005.00267.x
18. Kalhan SC. Protein metabolism in pregnancy. *Am J Clin Nutr*. 2000;71(5 Suppl):1249S-1255S. doi:10.1093/ajcn/71.5.1249s
19. Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. *Endocrinol Metab Clin North Am*. 2011;40(4):795-826. doi:10.1016/j.ecl.2011.08.002
20. Clifford-Mobley O, Sjogren A, Lindner E, Rumsby G. Urine oxalate biological variation in patients with primary hyperoxaluria. *Urolithiasis*. 2016;44(4):333-337. doi:10.1007/s00240-016-0860-2