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Pregnancy and Breastfeeding in Nephropathic Cystinosis With Native Kidneys

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Received 10 March 2022; revised 3 May 2022; accepted 13 May 2022; published online 19 May 2022

Kidney Int Rep (2022) **7,** 1716–1719; https://doi.org/10.1016/j.ekir.2022.05.013

INTRODUCTION

Cystinosis is an autosomal recessive disorder causing deficiency of cystinosin, a lysosomal cystine transporter.[1] Patients with cystinosis develop complications from cystine accumulation, such as Fanconi syndrome, progression to kidney failure, retinopathy, and endocrine disorders.[2] Early and adequate cysteamine treatment, which reduces intracellular cystine levels, can reduce the rate of kidney disease progression.[3] There are 11 published cases of cystinosis in pregnancy,[4–7] 10 in women who were dialysis-dependent or had undergone kidney transplantation before pregnancy.

Because of paucity of data for cysteamine use in pregnancy and breastfeeding, there are currently no recommendations to guide decision-making. Most women in previously published cases have chosen to discontinue cysteamine during pregnancy and avoid breastfeeding after resuming treatment.[4,5]

We present a case of a woman with cystinosis and preserved native kidney function who underwent a successful pregnancy and breastfed after resuming cysteamine. This is the first known report containing data on breastmilk cysteamine concentrations.

CASE PRESENTATION

A 24-year-old woman with infantile nephropathic cystinosis and stage G2A3 chronic kidney disease (CKD) was referred for preconception counseling. Cystinosis was confirmed by an elevated leucocyte cystine level in infancy. Early diagnosis, made possible by cystinosis in an older sibling, and good treatment adherence contributed to delayed kidney disease progression. Electrolyte abnormalities secondary to Fanconi syndrome were treated with daily supplemental dosages of potassium 96 mmol, phosphate 25.2 mmol, and sodium bicarbonate 53.6 mmol. There were no overt extra-renal complications apart from mild photophobia. Her average prepregnancy urine protein-to-creatinine ratio was 132 mg/mmol, α1-microglobulin-to-creatinine ratio was 30.7 mg/mmol, and estimated glomerular filtration rate (eGFR) was 89 ml per minute per 1.73 m^2. On confirmation of pregnancy, losartan and cysteamine were discontinued. Low-dose aspirin was initiated for the prevention of pre-eclampsia.

As expected, proteinuria and eGFR increased during pregnancy.[8] Blood pressure remained normal with no evidence of gestational hypertension or pre-eclampsia. Daily electrolyte supplementation increased to potassium 128 mmol and phosphate 33.6 mmol, with no increase in the dose of sodium bicarbonate. Average leucocyte cystine increased from 0.15 nmol $^1/_2$ cystine per mg protein to 4 nmol $^1/_2$ cystine per mg protein.

The pregnancy was complicated by recurrent urinary tract infections (UTIs) in the first and second trimesters, and a complicated UTI at 29 weeks with *Staphylococcus epidermidis* bacteriuria and bacteremia.

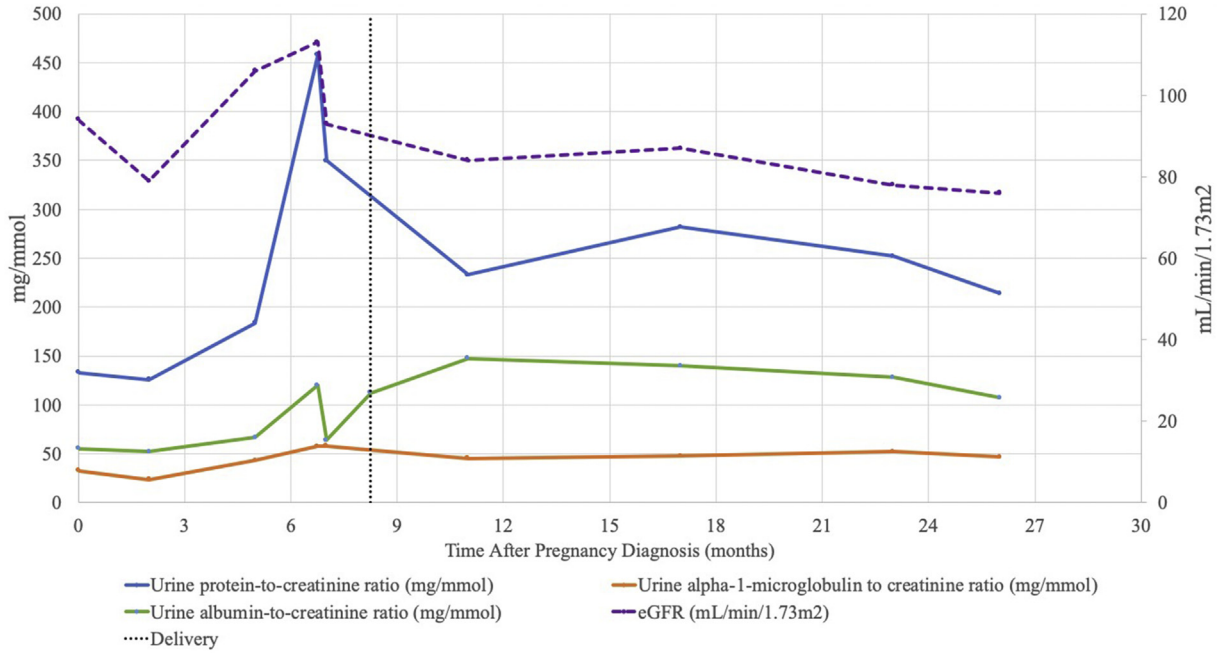

Figure 1. Urinary proteins and eGFR at baseline, during pregnancy and postpartum. eGFR, estimated glomerular filtration rate.

After treatment of the complicated UTI, prophylactic oral antibiotics were administered for the remainder of pregnancy without UTI recurrence.

She developed spontaneous preterm rupture of membranes at 33 weeks and 1 day gestation, and delivered a male infant who weighed 1886 g via spontaneous vaginal delivery. Apgar scores were 4, 7, and 9 at 1, 5, and 10 minutes. The infant was admitted to the neonatal intensive care unit for 23 days.

Cysteamine was reinitiated immediately after delivery and enalapril was initiated at 2 weeks postpartum. The postpartum proteinuria stabilized at a level higher than the prepregnancy values, and α1-microglobulin-to-creatinine ratio and eGFR were stable (Figure 1).

While breastfeeding, her delayed-release cysteamine dosage was 675 mg twice daily (0.84 mg/m^2/d) compared with her prepregnancy dosage of 825 mg twice daily (1.06 mg/m^2/d). The cysteamine dosage was reduced during breastfeeding as a precaution because of the lack of lactation safety data. She exclusively breastfed for 4 months and discontinued at 5 months. The cysteamine dosage subsequently stabilized at 750 mg twice daily (0.95 mg/m^2/d).

Table 1. Breastmilk cysteamine concentration relative to dose of delayed-release cysteamine bitartrate at steady state

Time postdose (h)	Breastmilk cysteamine concentration (mg/l)
0	0.12
2	0.76
4	1.87
6	0.51

Breastmilk samples were collected and analyzed (Table 1 and Supplementary Methods). The calculated relative infant dose was 0.4%. The predicted infant cysteamine dose over 24 hours was 0.52 mg. Infant cysteamine levels were not measured. The infant had normal growth and development at 18 months and a normal leucocyte cystine level.

DISCUSSION

As a result of early diagnosis and cysteamine availability, a higher proportion of individuals with cystinosis are entering the third decade of life without the need for kidney replacement therapy.[2] This has implications for women of reproductive age, with cystinosis and CKD in native kidneys, who desire pregnancy.

There are no human studies on the risk of developmental toxicity secondary to cysteamine. A study on pregnant rats demonstrated a dose-dependent relationship, reporting a significantly increased risk of intrauterine death, intrauterine growth restriction, cleft palate without cleft lip, and kyphosis at doses 1.7 times the recommended human dose.[9,S1] There is one published case in which cysteamine was continued through pregnancy with no reported major birth defects[S2]; all others discontinued use.

In patients with cystinosis who have undergone kidney transplantation, the decision to hold oral cysteamine during pregnancy is generally straightforward. Although the risk for progression of extra-renal complications remains, there are excellent long-term outcomes for graft survival because cystine transport is normal in the grafted kidney.[S3]

Table 2. Teaching points

Pregnancy and breastfeeding in cystinosis
• Preconception counseling is necessary in women with CKD and should include a discussion regarding use of renal protective medications, delaying pregnancy if kidney transplantation is anticipated in the near future, and strategies to reduce the risk of pre-eclampsia.
• Regular monitoring of kidney function and frequent discussion with the patient and multidisciplinary care team can aid decision-making about reinitiation of cysteamine during pregnancy.
• Low amounts of cysteamine were detected in breastmilk and are unlikely to be clinically significant. This is reassuring for individuals with cystinosis who desire to breastfeed, including in resource-limited settings where replacement feeding may be less accessible.

CKD, chronic kidney disease.

Nevertheless, for patients with native kidneys, the benefits and risks of continuing treatment in pregnancy should be weighed.

Prepregnancy kidney function may guide these decisions; the greater the degree of kidney impairment, the higher the likelihood of kidney function decline during pregnancy that may persist or progress to kidney failure.[8] Despite the unknown safety of oral cysteamine in pregnancy, patients may opt to resume treatment in the second or third trimester after organogenesis to minimize the risk of kidney injury. This discussion is particularly important for individuals with native kidneys who desire multiple pregnancies. In this case, our patient decided to remain off cysteamine because her eGFR remained stable during pregnancy. The clinical significance of the increased proteinuria at 1-year postpartum is unclear; it may suggest mild progression of underlying CKD. The stability of her α1-microglobulin-to-creatinine ratio supports no major change to proximal tubular function.

In previously published cases of cystinosis in pregnancy, pre-eclampsia and preterm delivery were common. It is challenging to distinguish between pregnancy outcomes associated with cystinosis alone and outcomes attributed to underlying CKD. Individuals with CKD have a greater risk of preterm delivery, small-for-gestational-age infants, pre-eclampsia, and perinatal death, which increases with the degree of kidney impairment.[8] Our patient's baseline risk for preterm delivery may have been further increased by the complicated UTI during the third trimester because symptomatic bacteriuria and UTIs are associated with preterm labour.[S4]

There are no data examining safety of oral cysteamine while breastfeeding. We present the first published data of breastmilk cysteamine concentrations for an individual taking cysteamine bitartrate. The calculated relative infant dose of 0.4% is reassuring; a relative infant dose <10% is considered acceptable for most medications in lactation.[S5] Moreover, the calculated infant cysteamine dose of 0.52 mg over 24 hours is clinically a small dose when compared with the therapeutic infant dosage of 60 to 90 mg/kg/d.[2]

CONCLUSION

Because of advances in diagnosis and treatment, cases of pregnancy in individuals with cystinosis and native kidneys may become more common. In our patient, there was increased proteinuria but stable eGFR and tubular function postpartum even though cysteamine was discontinued during pregnancy. It is essential that these patients undergo preconception counseling and pregnancy planning to reduce the risk of complications. Our data demonstrate low amounts of cysteamine in breastmilk that are unlikely to be clinically significant, which is reassuring for women with cystinosis who desire to breastfeed (Table 2). More data are needed to confirm the safety of cysteamine use in breastfeeding.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

Patient consent was obtained.

ACKNOWLEDGMENTS

The authors thank our patient for providing consent for publication to share this information with the medical community and other individuals who have cystinosis.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

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