

A Successful Adolescent Pregnancy in a Patient With Cystinosis and CKD Not Yet on Kidney Replacement Therapy



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INTRODUCTION

Cystinosis is a rare autosomal recessive lysosomal storage disorder. It is caused by biallelic mutation of the CTNS gene that encodes for cystinosin, a lysosomal cystine efflux transporter.¹ This results in accumulation, precipitation, and crystallization of cystine within the lysosomes,^{S1} leading to lysosomal dysfunction via oxidative stress and apoptosis.^{S2,S3} Cystinosis most commonly presents with a renal Fanconi syndrome that is usually evident in the first year of life. It initially presents with failure to thrive and later manifests with hypophosphatemic rickets and chronic kidney disease with nephrocalcinosis.^{1,2} Other extrarenal manifestations include photophobia because of corneal cystine deposition, hypothyroidism, hypogonadism, diabetes, myopathy, and visual and spatial cognitive dysfunction.¹

With effective treatment, patients with cystinosis live longer. To our knowledge, this is the first case report describing a successful pregnancy in a patient with cystinosis and chronic kidney disease before kidney replacement therapy (KRT). This case report documents the challenges and management of a young woman with cystinosis during her pregnancy.

CASE PRESENTATION

Background

The patient presented to pediatric nephrology at 2 years with a delay in her gross motor milestones, including walking. Her weight and height were below the third centile (−3 Z score). She had hypophosphatemia rickets

and renal Fanconi syndrome, which was suggestive of cystinosis. Her diagnosis was confirmed by elevated plasma leucocyte cystine levels of 5.67 nmol cystine per mg protein (normal <0.1 nmol cystine per mg protein) and corneal cystine crystals on slit-lamp examination. Genetic testing confirmed the CTNS gene mutation (c.971-12G>A), which is the most common mutation seen in the South African Black population. Cysteamine suspension and eye drops were commenced.

Counseling

At 17 years, the patient presented to pediatric nephrology, 18 weeks pregnant. Her creatinine level before pregnancy was 76 μmol/l and estimated glomerular filtration rate Schwartz method was 62.0 ml/min per 1.73 m². This was an unplanned but wanted pregnancy. She was referred through to a multidisciplinary obstetrical team that included a maternal and fetal medicine specialist and a geneticist. She and her family were extensively counseled regarding risks to maternal and fetal well-being. She was counseled regarding the teratogenic risks of cysteamine exposure and the risk of accelerated deterioration of her renal function with stopping cysteamine. This was emphasized because KRT in the state sector of South Africa is limited owing to resource constraints. The patient and her family decided to pursue the pregnancy, and cysteamine was stopped. She did not require KRT before, during, or after her pregnancy.

Transition to Adult Service

The patient was transitioned to the adolescent nephrology clinic at 24-week gestation. After

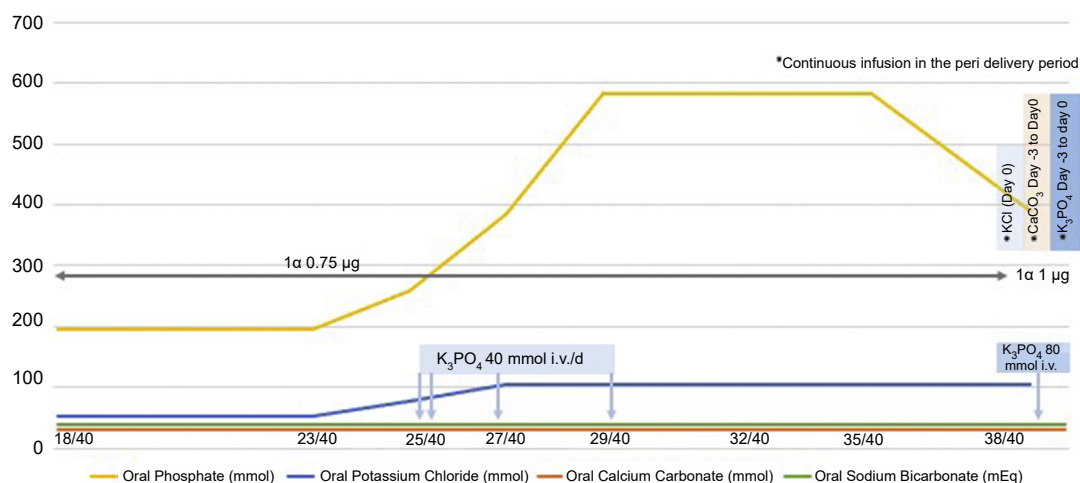


Figure 1. Supplementary electrolyte doses throughout pregnancy. CaCO_3 , calcium carbonate; K_3PO_4 , potassium phosphate; KCl, potassium chloride; mEq, milliequivalent.

cysteamine cessation, her leucocyte cystine level rose from 1.22 to 3.27 nmol cystine per mg protein. A multidisciplinary kidney and obstetrical team co-managed and optimized her electrolyte derangements. Blood pressure, creatinine levels, electrolytes, and a 24-hour urine protein collection were checked at every visit.

Her electrolyte abnormalities and requirements (particularly potassium and phosphate levels) increased throughout the pregnancy. Adherence was a challenge because of her medication load and side effects (e.g., diarrhea). **Figure 1** describes the initial treatment and medication adjustments. Lower doses but more frequent dosing schedule of oral phosphate (Sandoz) 2 tablets (32 mmol), 2-hourly, helped to relieve side effects and improve tolerance. Other pregnancy-related complications included severe back pain, which required physiotherapy and a walker to assist her mobility.

She was reviewed every second week at the high-risk obstetrical antenatal clinic until 34 weeks and thereafter weekly until delivery at 38 weeks. Clinically, she coped well and her kidney function remained stable. Fetal growth and well-being were monitored closely and were in keeping with a constitutionally small baby rather than intrauterine growth restriction. Her amniotic fluid index and umbilical artery Doppler results remained normal throughout the pregnancy. In planning for her delivery, given her rickets, height of 130 cm, and high risk for cephalopelvic disproportion, she was offered an elective cesarean section (C/S) under general anesthesia. Future family planning included an intrauterine contraceptive to be placed at C/S.

The patient was admitted at 38 weeks for elective C/S and kept nil-per-mouth prior, which resulted in hypokalemia and hypophosphatemia. This required aggressive i.v. correction of potassium phosphate and calcium gluconate infusion every 6 hours. Her C/S was

delayed owing to significant electrolyte requirements. Postoperatively, she was carefully monitored in the obstetrical intensive care unit for 24 hours. The neonatal outcome was a healthy male infant (2415 g, z score -1 ; length 50 cm, z score -1 ; head circumference 38 cm, z score 0, suggesting constitutional small infant) with good Apgar scores. He was assessed by the neonatology and pediatric nephrology service, and no evidence of cystinosis was found. Urine dipstick result was clear, and blood test results showed normal electrolyte levels with no features of renal Fanconi syndrome. The leucocyte cystine level of the infant was unfortunately insufficient on 2 episodes. Genetic testing was offered but not yet done. After much discussion, the patient was advised to breastfeed in view of the clear overall benefits of breastfeeding in a low-resourced environment. Cysteamine was restarted at 500 mg 12 hourly within a week of delivery. Oral supplementation of potassium and phosphate was reduced to potassium chloride 26 mmol (3.5 tablets) 8 hourly and phosphate 65 mmol (4 tablets) 8 hourly. The patient's creatinine level 2 months after delivery was 95 $\mu\text{mol/l}$ (estimated glomerular filtration rate 55 ml/min per 1.73 m^2).

DISCUSSION

To best of our knowledge, this is the first case report of an adolescent patient with cystinosis, who became pregnant before KRT, with an outcome of healthy mother and baby. These are high-risk complex pregnancies. **Table 1** describes available literature of 10 case reports, describing outcomes of cystinosis pregnancies on KRT (including transplant). Most described preterm gestation that varied from 24 to 38 weeks, and most delivered by C/S.^{3–9} A total of 6 of the patients

Table 1. Ten case series of maternal and fetal outcomes in cystinosis-related pregnancies^{3–8}

	Reiss <i>et al.</i>	Andrews <i>et al.</i>	Haase <i>et al.</i>	Ramappa <i>et al.</i>	Chuang <i>et al.</i>	Lindsay <i>et al.</i>	Blakey <i>et al.</i>	Blakey <i>et al.</i>	Kuczborska <i>et al.</i>	Robertson <i>et al.</i>
Country	USA	United Kingdom	Germany	United Kingdom	Taiwan	USA	United Kingdom	United Kingdom	Poland	South Africa
Maternal age (yr)	20	30	21	Not known	25	31	26	33	27	17
CKD/KRT modality before pregnancy	Transplant	Transplant	HD	HD	Transplant	HD Previous TXP	Transplant	Transplant	Transplant	CKD
Prepregnancy eGFR (ml/min per 1.73 m ²)	—	—	—	—	88	—	74	40	—	—
Proteinuria (mg/mmol)	—	—	—	—	—	—	ACR 9.5 mg/mmol	ACR 3.6 mg/mmol	—	UPCR 336 mg/mmol
Cysteamine before pregnancy	No	Yes	Yes (remained on during pregnancy)	Yes	No	Unknown	Yes	Yes	Yes	Yes
Gestation (wk + d)	35 + 3	33 + 5	31 + 5	25	Not known	24 + 2	37 + 4	29 + 5	32	38
Mode of delivery	Cesarean section	Cesarean section	NVD	NVD	NVD	Cesarean section	Cesarean section	Cesarean section	Cesarean section	Cesarean section
Maternal outcome	PE	PE, CPD	Premature ROM	Pregnancy-related CMO	None	—	None	Intrapartum AKI PE	PE	None
Fetal outcomes	—	—	Polyhydramnios	Stillbirth	None	Death (severe bronchopulmonary dysplasia)	None 3374 g	Preterm 1207 g	1400 g	None
NICU, wk	No	No	3 d	N/A	No	16 wk	10 d	8 wk	3 wk	No
Neonate feeding status	—	—	—	N/A	—	—	Bottle fed (reinitiated cysteamine)	—	—	Breast feeding (reinitiated cysteamine)

ACR, albumin creatinine ratio; AKI, acute kidney injury; CKD, chronic kidney disease; CMO, cardiomyopathy; CPD, cephalopelvic disproportion; eGFR, estimated glomerular filtration rate; HD, hemodialysis; KRT, kidney replacement therapy; N/A, not applicable; NICU, neonatal intensive care unit; NVD, normal vaginal delivery; PE, pre-eclampsia; ROM, rupture of membranes; TXP, transplant; UPCR, urinary protein-to-creatinine ratio; USA, United States of America.

experienced maternal complications, the most common being pre-eclampsia.^{3-6,8,9}

There are limited data available on pre- and post-delivery estimated glomerular filtration rate and proteinuria. The patient had a significant urine protein-to-creatinine ratio of 0.336 g/mmol before pregnancy. Postpartum, her creatinine level was 97 $\mu\text{mol/l}$, estimated glomerular filtration rate Schwartz method of 49 ml/min per 1.73 m², and her urine protein-to-creatinine ratio was 0.4 g/mmol.

Important Pharmacologic Considerations During the Antenatal Period

Cysteamine treatment guidelines recommend the continuation of cysteamine treatment in transplanted patients and those on dialysis.⁵⁴ The recommended dose for cystine reduction therapy with immediate-release cysteamine compounds is 2 g/d for patients > 12 years of age or weighing >50 kg. Furthermore, maximum recommended proposed dosing based on body surface area in adults is 1.95 g/m²/d, but limited data are available.⁵⁴

Owing to the prohibitive cost, South Africa does not have the tablet formulations of cysteamine, that is, Cystagon or Procsybi, which are available in high-income countries. As an alternative, our pharmacies have manufactured a suspension, (cysteamine chloride powder [from China] constituted into cysteamine solution), which is unfortunately highly unpalatable



Figure 2. Cysteaminium chloride powder used for formulation of cysteamine suspension in South Africa.

(Figure 2). This affects adherence, owing to poor taste and frequent dosing requirements (ideally every 6–8 hours), exacerbating the high medication burden. Monitoring of this disease is recommended with a serum leucocyte cystine level every 3 to 6 months.

Potential teratogenicity of cysteamine has been found in animal models. These include cleft palate, kyphosis, ventricular septal heart defects, microcephaly, and exencephaly.⁷ It is therefore recommended to stop cysteamine during pregnancy. The implication is the accumulation of cystine, which can accelerate the progression of cystinosis and may also adversely affect uteroplacental function.⁵⁵ Only 1 mother in the case series outlined in Table 1 continued cysteamine during pregnancy.

Considerations Postdelivery in a Resource-Limited Environment

The extent to which cysteamine treatment is excreted in the breast milk is unknown. Most guidelines recommend not breastfeeding to minimize the cysteamine-free period.⁵⁶ However, there is an alternative view on breastfeeding. Some studies have shown very low (i.e., micromolar range) cysteamine concentrations in the plasma and thus minimal concentrations in the breast milk. Hence, toxicity is unlikely⁵⁷ (personal communication with Prof. Elena Levtchenko, University of Leuven, Belgium).

The decision on breastfeeding should consider a patient's social circumstances. In a low-resource environment with food and clean water insecurity, the benefits of breastfeeding far outweighed the risks of cysteamine toxicity, which seem minimal.

CONCLUSION

This case report describes a pregnancy in a patient with cystinosis with chronic kidney disease, not yet on KRT, with successful outcome to mother and baby. With improved treatment for cystinosis, adult nephrologists and obstetricians need to be aware of the management of these extremely complicated patients (Table 2).

Table 2. Teaching points

Number	Teaching point
1	Prepregnancy counseling should be available for patients of childbearing age
2	Maternal and fetal considerations include a high risk of pre-eclampsia and preterm delivery by cesarean section.
3	Fetal growth spurt is associated with increasing electrolyte requirements and peridelivery electrolyte abnormalities, which need to be managed carefully.
4	Prolonged periods of perioperative fasting result in worsening electrolyte abnormalities that may delay surgery.
5	Breastfeeding may be the safest option in a resource-limited setting.
6	Adult nephrologists and obstetricians need to be aware of the management of these patients as they are surviving into adulthood.

DISCLOSURE

The authors declared no competing interests.

PATIENT CONSENT

The patient provided written informed consent for this publication.

SUPPLEMENTARY MATERIAL

[Supplementary file \(PDF\)](#)

Supplementary References.

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