ORIGINAL ARTICLE

Pregnancy in cystinosis patients with chronic kidney disease: A European case series

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Abstract

Cystinosis is a rare autosomal recessive disease leading to end-stage renal disease within the second or third decade of life. Since the era of specific treatment with cysteamine, prognosis has substantially improved and pregnancy becomes an increasing concern. Pregnancy data in patients with cystinosis were collected through an anonymized survey. We collected data for 19 pregnancies in 12 women. Seventeen patients were transplanted, 1 was on hemodialysis and 1 had chronic kidney disease (CKD) stage 4. These 19 pregnancies resulted in 13 live births (68.4%): 3 spontaneous early miscarriages, 1 ectopic pregnancy, 1 early pre-eclampsia (at 21 weeks), and 1 preterm birth with neonatal death at 24 weeks were reported. After exclusion of early miscarriage or termination, pregnancy success rate was 86.7%. In successful pregnancies, median gestational age at delivery was 34 weeks (24–37). Preeclampsia occurred in seven pregnancies (7/15, 46.7%). A cesarean section was performed in all pregnancies. Median baby weight at delivery was 2175 g (620–3374 g). After pregnancy, one patient reached end-stage renal disease, but she already had advanced CKD before pregnancy (creatinine 239 μmol/L, eGFR 23 ml/min/1.73 m^2). In three other patients, there was a decrease of eGFR of 8, 20, and 53 ml/min/1.73 m^2, respectively. The majority of pregnancies were

successful, but severe antenatal and post-natal complications may occur, in particular preeclampsia that was noticed in nearly half of patients and fetal loss in one-third of them. These results may help pre-pregnancy counseling and pregnancy management.

KEYWORDS

cesarean section, cysteamine, cystinosis, pre-eclampsia, pregnancy, renal transplantation

1 | INTRODUCTION

Cystinosis is a rare autosomal recessive disease characterized by a widespread cystine deposition, leading to Fanconi syndrome and end-stage renal disease within the second or third decade of life. Extra-renal manifestations such as hypothyroidism, diabetes mellitus, and myopathy may also develop. Since the era of specific treatment with cysteamine and renal transplantation, prognosis of cystinosis patients has changed and more than half of the patients are now adults. Pregnancy is an increasing concern for this patients' group.

The first successful pregnancy in a female with cystinosis was reported in 1988 by Reiss et al in a transplanted patient with unusual histopathological finding of cystine crystals packed in the maternal portion of the placenta.[1] Then, a few other reports have been published in transplanted or in dialysis patients.[2–5]

Due to its rarity, few outcome data exist to inform prognosis and management of pregnancies in these patients to guide women during pre-pregnancy counseling. It is likely that there is an under-reporting of pregnancy losses and/or adverse pregnancy outcomes. A European initiative of reference networks for rare diseases was launched to allow expansion of the current evidence base and to share knowledge and experience in managing these pregnancies across centers. As part of the European Rare Kidney Disease Reference Network (ERKNet) and together with the European Renal Association (ERA) working group on inherited kidney diseases (WGIKD), we aimed to collect data on pregnancy in women with cystinosis in a multinational cohort of cystinosis patients.

2 | MATERIALS AND METHODS

2.1 | Clinical data

An anonymized online survey was sent to the membership of ERKNet, UK rare disease working group (RDWG), ERA, and the cystinosis community, inviting clinicians to provide data on cystinosis patients who had a pregnancy. A total of 81 questions were asked, pertaining to demographics, treatment, kidney function, complications, as well as pregnancy and delivery outcome. A list of all questions is provided in Table S1. Data were collected locally from patients' notes and biology results systems according to local ethical requirements. In case of missing information or if the provided data points were noted to be outliers, the corresponding clinicians were contacted via e-mail for completion and/or verification of data. Two patients were already published.[2]

2.2 | Study inclusion criteria

Women with diagnosis of infantile nephropathic cystinosis (clinical and/or genetic diagnosis) and confirmed pregnancies were included (including termination of pregnancy/miscarriage/still births). Study conduct complied with the Declaration of Helsinki Principles.

3 | RESULTS

3.1 | Patients

We collected data on 19 pregnancies in 12 cystinosis patients (including 2 pregnancies in 3 women and 3 pregnancies in 2), in seven European centers: Paris Necker, France (6), Birmingham, United Kingdom (5), Nijmegen, Netherlands (4), Leuven, Belgium (1), Lyon, France (1), Clinica Universidad de Navarra, Spain (1), and Rome, Bambino Gesu, Italy (1).

3.2 | Maternal characteristics

Median age at cystinosis diagnosis was 1.4 years (range 0.5–4.0) and median age at specific treatment by cysteamine start was 3.7 years (range 1.0–38.0; Table 1 and Table S2). Median height was 150.5 cm (range 122.0–159.0) and median weight before pregnancy 53.4 kg (range 30.0–60.0). Median age at pregnancy was 28.5 (21–36) years.

TABLE 1 Pre-pregnancy maternal characteristics

N pregnancies	19
Maternal age (years)	28.5 (21–36)
Age at cystinosis diagnosis (years)	1.4 (0.5–4.0)
Height (cm)	150.5 (122.0–159.0)
Weight (kg)	53.4 (30.0–60.0)
Diabetes mellitus	2 (10.5%)
Hypertension	12 (63.2%)
Pre-pregnancy CKD stage	
1–3	0
4	1 (5.3%)
5	18 (94.7%)
Renal replacement modality for CKD 5	
Hemodialysis	1 (5.6%)
Kidney transplant	17 (94.4%)
Pre-pregnancy serum creatinine (μmol/L)	121 (53–329)
Pre-pregnancy eGFR (ml/min/1.73 m^2)	50 (23–111)
Pre-pregnancy urine protein/ creatinine ratio (mg/mmol)	7 (0–61)
Cysteamine stopped?	
Pre-pregnancy	7 (36.8%)
On confirmation of pregnancy	11 (57.9%)
Later in pregnancy	1 (5.3%), at 5 weeks
Continued through pregnancy	0

Note: Median (range), *N*, number (percentage).
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate by MDRD.

Two patients presented with diabetes mellitus before pregnancy and seven patients with hypothyroidism (one of them had three pregnancies). Swallowing impairment was detected in two patients and one of them had two pregnancies. These two patients also had a myopathy. A patient who had three pregnancies had a respiratory muscle weakness.

Precise genetic data were available in six patients. Three patients carried the European 57 kb deletion at the homozygous state, two at the heterozygous state, in association with another severe mutation, and one patient carried the G339R mutation (exon 12) at the homozygous state.

3.3 | Pre-pregnancy renal characteristics

All patients but one had reached end-stage renal disease before pregnancy. One patient was on hemodialysis and the others were transplanted. Renal function before

TABLE 2 Maternal outcome

Outcome	*n* = 19 pregnancies
Live birth	13 (68.4%)
Pregnancy failure	
Spontaneous early miscarriage	3 (15.8%)
Ectopic pregnancy	1 (5.3%)
Early pre-eclampsia (21 weeks)	1 (5.3%)
Pre-term with neonatal death	1 (5.3%)
Pre-eclampsia	7/15 (46.7%)
Gestational diabetes	2/15 (13.3%)
Induction of labor	14/15 (93.3%)
Serum creatinine 6 months postpartum (μmol/L) 1 patient with stage 4 CKD pre-pregnancy progressed to ESRD post-pregnancy	129 (66–400)
eGFR 6 months postpartum (ml/min)	43.0 (11.6–114.0)

Note: Median (range), *N*, number (percentage).
Abbreviation: eGFR, estimated glomerular filtration rate by MDRD formula.

pregnancy was defined by a median serum creatinine at 121 μmol/L (53–239) or a median estimated glomerular filtration rate (eGFR) by MDRD at 50 ml/min/1.73 m^2 (23–111). Median proteinuria before pregnancy was 7 mg/mmol creatininuria (range 0–61). In 12 pregnancies (63.2%), the patients were treated for high blood pressure before pregnancy. In 17 out of 19 pregnancies, a pre-pregnancy counseling was performed before pregnancy. All patients but one were given contraceptive advice. Assisted conception was used in one case.

All patients were treated with cysteamine before pregnancy. Specific treatment with cysteamine was stopped before pregnancy in seven cases, on diagnosis of pregnancy in 10, after 5 weeks of pregnancy in one patient, and continued in one case who finally experienced miscarriage.

3.4 | Maternal outcome

All but one pregnancy were spontaneous. Thirteen live births were observed after these 19 pregnancies (68.4%; Table 2 and Table S1). Three spontaneous early miscarriages (before 12 weeks), 1 ectopic pregnancy, 1 early pre-eclampsia (at 21 weeks), and 1 preterm birth with neonatal death at 24 weeks were reported. One patient who presented with miscarriage was a dialysis patient who required in vitro fertilization. After exclusion of early miscarriage or termination, pregnancy success rate was 86.7%. Low-dose acetylsalicylic acid treatment was

TABLE 3 Fetal and child outcome

Live births	13 (68.4%)
Gestational age (weeks)	34 (24–37)
Birth weight (g)	2175 (620–3374)
Requirement for neonatal intensive care unit	5 (38.5%)
Mode of feeding	
Breast	2 (15.4%)
Bottle	11 (84.6%)
Age of infant at last follow-up (years)	3.9 (0.5–35.0)

Note: Median (range), N, number (percentage).

given during seven pregnancies, together with enoxaparin in two pregnancies in the same patient. In 10 pregnancies, blood pressure control worsened during pregnancy. No infection was observed.

In successful pregnancies, median gestational age at delivery was 34 weeks (24–37). Preeclampsia was diagnosed in seven pregnancies in 15 patients (7/15, 46.7%), including HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome in 1 (1/15, 6.7%). There was no difference in mother age, pre-pregnancy eGFR, proteinuria, hypertension, or low dose acetylsalicylic acid treatment between patients who presented with preeclampsia and those who did not. Gestational diabetes was diagnosed in two patients. A severe anemia (below 9 g/dl) was observed in four patients, including two who required erythropoietin treatment. Onset of labor was spontaneous in only one case. A cesarean section was performed in all patients (13/13, 100%) due to prematurity and/or preeclampsia. One patient required ventilation post-partum in the setting of pre-eclampsia and pre-existing respiratory muscle weakness. There was no correlation between complications and genotype. We analyzed the duration of cysteamine treatment and its impact on pregnancy outcome. The four patients who started cysteamine the latest (at 38, 29, 17, and 13 years of age) and who had the shortest duration of treatment until pregnancy (0, 2, 8, and 15 years) had a successful outcome of the pregnancy (Table S1).

Median serum creatinine 6 months after pregnancy was stable at 129 µmol/L (66–400) with a median percentage of increase of serum creatinine of 1.7% (0%–92.2%). Median eGFR was 43.0 ml/min (11.6–114.0), corresponding to a 5.3 ml/min median eGFR decrease. One patient reached end-stage renal disease and started hemodialysis 6 months after delivery. Pregnancy may have accelerated eGFR decrease, but she already had advanced CKD before pregnancy (serum creatinine 239 µmol/L, eGFR by MDRD 23 ml/min/1.73 m^2) and no

superimposed preeclampsia was associated with this decrease. In three other patients, a significant increase of serum creatinine by 20.3%, 32.3%, and 92.2%, respectively, and a decrease of eGFR of 8, 20, and 53 ml/min/1.73m², respectively, were observed.

Breast feeding was chosen after her two pregnancies by the same woman not taking cysteamine during that period. The other women used bottle feeding.

3.5 | Fetal outcome

Median baby weight at delivery was 2175 g (620–3374; Table 3). Neonatal intensive care was required in five cases, for a median duration of 8 weeks (1.4–14). Children were healthy at a median age at last follow up to 3.9 years (0.5–35).

4 | DISCUSSION

Improvement of care for patients with cystinosis, including specific treatment with cysteamine, progress in dialysis, and renal transplantation, has resulted in an increasing number of patients with few complications at adult age.[6] In the last years, pregnancy has thus emerged as a major concern for adult cystinosis women. We report here the largest series of pregnancies in patients with cystinosis showing the successful outcomes, but also a high frequency of complications.

A pubertal delay was observed in female cystinosis patients before the era of cysteamine treatment.[7,8] The protective effect of an early cysteamine treatment on gonads in females was shown by Broyer et al.[9] Several successful pregnancies have been described.[1–5]

As in all patients with renal failure or in transplanted patients, pregnancies in cystinosis patients need multidisciplinary pre-conception planning and ante-natal follow-up. Drugs have to be adapted before conception and close monitoring is required. While cysteamine is the specific treatment of cystinosis having demonstrated beneficial long-term effects on renal and extra-renal complications, and mortality, it is recommended to stop it during pregnancy because of potential teratogenicity, as it was done for all patients in this series.[6,10] Cysteamine has proven to be teratogenic in rats and produces dose-dependent developmental toxicity at high doses above 75 mg/kg/day during organogenesis and histogenesis. Specific malformations are associated with its use (cleft palate, kyphosis, vertebral anomalies), as well as intrauterine growth retardation and fetal death at 100–150 mg/kg/day.[11] Of note, the maximum therapeutic dose in humans is 1.95 g/m²/day (~60 mg/kg/day in adults). Beneficial

effect of cysteamine is a long-term effect and a short interruption of treatment should not have major consequences. Despite these toxicity data in animals, one human pregnancy on oral cysteamine has been reported without reported side effect on newborn.[3] In our series, some patients stopped the treatment before conception and others after diagnosis of pregnancy. An evaluation of the effects of cysteamine on early development in rats revealed no adverse effects on conception and early embryonic development.[12] As the time to conception can be protracted and because of the lack of congenital abnormalities in babies whose mothers stopped cysteamine at conception, we suggest stopping cysteamine treatment only on confirmation of pregnancy. Only one patient not taking cysteamine during that period breast fed her two babies. In the mothers treated with cysteamine, the excretion of the drug in breast milk remains unknown. The expected concentration of cysteamine in breast milk should be very low, but plasma levels in babies and the tolerance of low "dose" of cysteamine from breast milk remain unknown. There are substantial overall benefits to mother and baby of breast feeding and delaying reintroduction of cysteamine for the period of breast feeding may also have a long-term adverse impact on maternal health. Breastfeeding or not should be discussed case by case.[13]

One of the main complications described here is pre-eclampsia that occurred in nearly half of the patients. This complication has already been reported in other patients with cystinosis.[1,2,4,14] This rate is slightly higher than in series of pregnancies in other kidney transplant patients where it is estimated between 8 and 45%.[15–17] In kidney transplant patients, pre-eclampsia mainly depends on the degree of renal dysfunction, hypertension, and the extent of proteinuria before pregnancy.[18] Median eGFR was slightly decreased in these patients (50 ml/min) and a majority of the patients were treated for high blood pressure but pre-pregnancy proteinuria was low. Two kidney transplant patients developed gestational diabetes (13%), a rate similar to the other kidney transplant patients (1%–21%).[19–21] Success rate of pregnancies is also comparable to other metabolic diseases even if these diseases are very diverse.[22]

All patients underwent a cesarean section mainly due to prematurity and/or preeclampsia. This rate is higher than in other kidney transplant patients.[20] In some patients, a cesarean section may also be indicated because of cephalopelvic disproportion due to maternal short stature but this was not reported in this study.[4] Cystine crystals packed in the maternal portion of the placenta were described in the first published case.[1] In one transplant patient, urinary tract infections were reported.[14] Acute cardiac failure was described in a cystinosis patient occurring early after stillbirth following an unplanned pregnancy.[23] We did not observe such complication in this series: this case probably represents pregnancy-associated cardiomyopathy rather than a direct involvement of cystinosis.

At the time of pregnancy, some patients had already developed some extrarenal complications of the disease. In particular, three patients presented with severe complications of cystinosis such as respiratory weakness, myopathy, or swallowing impairment. The patient with respiratory weakness required ventilation in post-partum suggesting the importance of a careful evaluation before pregnancy.

This study has some limitations. It is a retrospective review in multiple centers, in Europe only, captured via an online form. There is probably an underestimation of miscarriage. Complications occurred in all age groups and were not correlated with age at initiation of specific treatment, but compliance to treatment was not assessed. However, this relatively large series significantly adds to the current knowledge regarding pregnancy in cystinosis.

5 | CONCLUSION

The majority of pregnancies in patients with cystinosis were successful, but severe antenatal and post-natal complications may occur, in particular preeclampsia and fetal loss. All patients required a cesarean section. These results may help pre-pregnancy counseling and pregnancy management in patients with cystinosis.

AUTHOR CONTRIBUTIONS

Aude Servais, Hannah Blakey, and Graham Lipkin contributed to conception, design, analysis, and interpretation of data. All authors contributed to drafting the article or revising it and provided intellectual content of critical importance to the work described. All authors gave final approval of the version to be published.

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CONFLICT OF INTEREST

Aude Servais and Elena Levtchenko declare consultancy fees for Chiesi and Recordati. Sandrine Lemoine declares consultancy fees for Chiesi. Mirian C. H. Janssen, Hannah Blakey, Paloma L. Martin-Moreno, Marcella Greco, David Game, and Graham Lipkin declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Availability of data and material statement: all data supporting the results are available at ERKNet central office and from corresponding author on request.

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SUPPORTING INFORMATION

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