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Review Article

Specificity of Nephrological Management of Women with Cystinuria

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Abstract

Cystinuria is the main cause of monogenic hereditary lithiasis, accounting for less than 1% of stones in adults and 3-4% of stones in children, with a very high recurrence rate of renal colic. Prevention of cystinuria recurrence in women differs from men because each moment of their lives includes specificities important to know because they expose the woman to many evitable but potentially deleterious complications under alcalinisation. During the childhood the girl is more exposed to the Urinary Tract Infections (UTI) than the young boy under the preventive alcalinisation because of his anatomia. The menarche time can expose the young woman to martial insufficiency that is mandatory to diagnose because it worsens the risk of severe UTI. The pregnancy has to be prepared at the preconceptionnal time by checking the stone free status by CT-scan to avoid severe complication like spontaneous abortion secondary to obstructive pyelonephritis or evitable premature childbirth because of the complication of the preexistent kidney stone with difficulties to manage the nephritic colic during this period. The pregnancy modifies the composition of the urines which become very lithogenic and can quickly lead to a coralliform stone even if there is only a small calcul before the pregnancy. The contraception has to be chosen with caution in these women at high risk of high blood pressure and chronic renal failure. The breastfeeding needs to be accompanied by a trained team. And the time of menopause because of the potentially severe hot flashes expose the cystinuric woman to dehydration with more highly frequent recurrences, and difficulties to maintain a efficient alcalinisation because of the frequent weight increase during the menopause, booth evitable when it is accompanied in an informed patient. The aim of this article is to describe the optimized management of women with cystinuria to prevent potentially severe complications.

Key Learning Points

Specific features in the management of women with cystinuria is associated with both their anatomy and different stages in life.

Cystinuria exposes women to iron deficiency and urinary tract infections, which must be investigated and treated.

These particularities help to educate young girls and women to prevent complications that are specific to their sex.

Keywords: Cystine Urolithiasis; Woman; Management

Introduction

Cystinuria (OMIM 220100) is the leading cause of monogenic urinary stone disease and accounts for less than 1% and 3-4% of stones in adults and children, respectively [1,2]. In its classic form, it is an autosomal recessive genetic disorder, which explains its high frequency in consanguineous populations. The prevalence of homozygous cases ranges from 1: to 9:100,000 but can vary from 1:2500 in Libyan-Jewish populations to 1:100,000 in Sweden [2]. The incidence of cystinuria is 1:7000 births worldwide [3]. In France, the incidence of homozygotes is approximately 1:20,000 births [4,5]. Cystinuria is linked to mutations in two genes—*SLC3A1* (Solute Carrier Family 3, member 1) and *SLC7A9* (Solute Carrier Family 7, member 9)—expressed in the proximal renal tubules and causes a transepithelial transport defect of dibasic amino acids, including cystine, ornithine, lysine, and arginine.

There are three recessive cystinuria-associated syndromes secondary to the deletion of the *SLC3A1* gene: hypotonia-cystinuria syndrome (OMIM 606407), which is linked to a deletion in the Prolyl Endopeptidase Like (PREPL) gene and characterized by growth retardation and minor facial dysmorphia [6]; atypical hypotonia-cystinuria syndrome, caused by the deletion of PREPL and chromosome 2 open reading frame 34 (C2orf34) genes and include mild to moderate mental retardation [7]; and 2p21 deletion syndrome, attributed to a homozygous deletion of PREPL, C2orf34, and protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1B (PPM1B) genes and consists of neonatal convulsions and mitochondrial dysfunction, which can lead to major difficulties in both the male and female sex [8]. Although the treatment approach is similar to classic cystinuria, hypotonia can impact an individual's ability to swallow.

Cystinuria is associated with an increased recurrence of renal colic, exceeding 90% in the absence of medical management and as high as 60% in treated patients [9,10]. Chronic kidney disease and hypertension are more prevalent in cystinuric patients than in the general population [2,11].

The principle treatment of stone prevention is alkaline hyperdiuresis; cystine precipitates at a physiological pH range between 5.5 and 6.5 and an optimal range between 7.5 to 8.0 is required to stay soluble. Since cystine can be hard to obtain, some nephrologists prescribe cystine-chelating substances, like captopril and thiol derivatives, which can be deleterious to women according to their stage in life. We want to inform clinicians of specific factors to take into consideration when treating women with cystinuria throughout life.

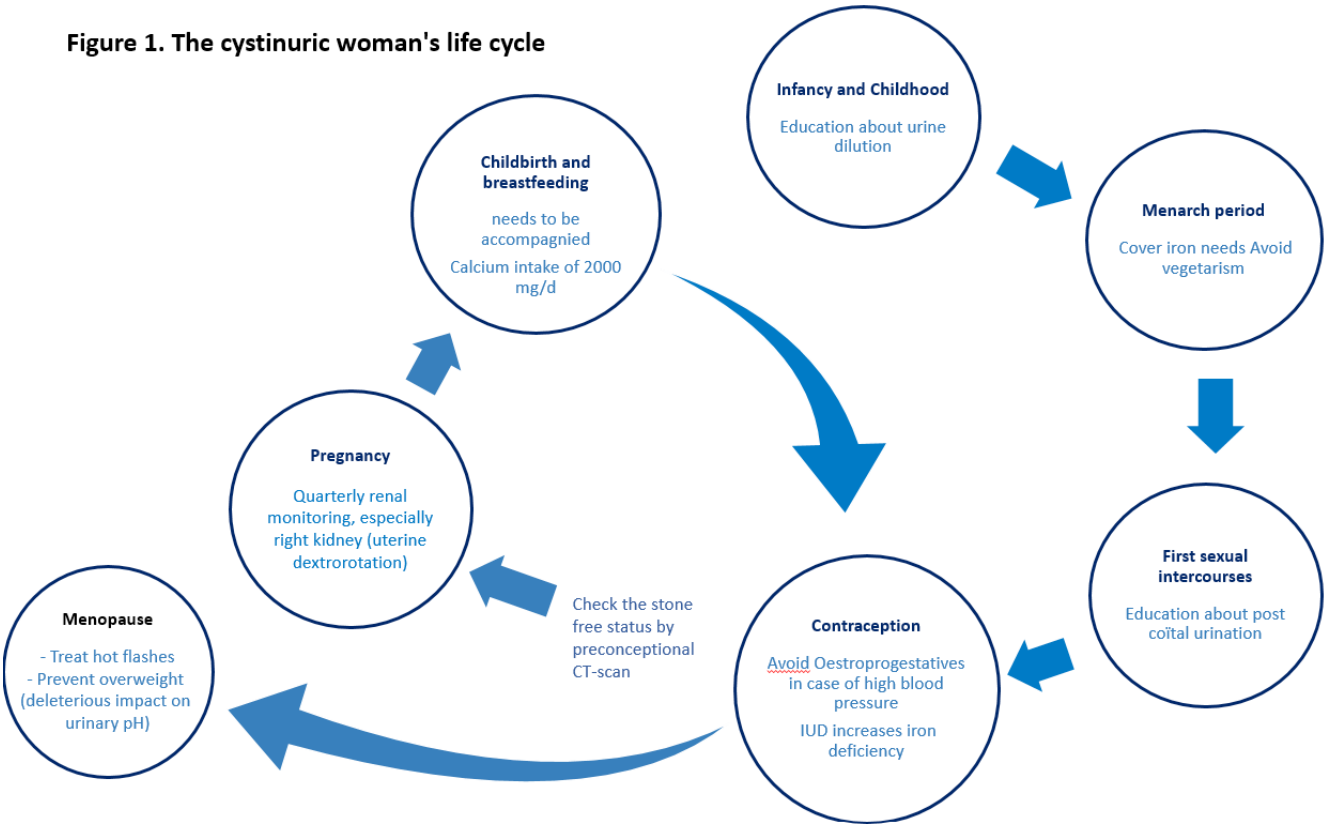
Urine alkalinization can increase the occurrence of urinary tract infections (UTIs) [12]. In cases with recurring UTIs, women with cystinuria often have iron deficiencies, with or without anemia. It is crucial to treat and correct iron deficiencies to prevent the recurrence of UITs (unpublished personal data). Thus, preventing recurrent cystine lithiasis in women differs from that in men (Table 1) [13]. Fluid intake volumes can be influenced by the various life stages of women. The aim of this article is to describe how to manage cystinuria in women, including specific features linked not only to their anatomy but also the different stages of life (Figure 1).

Points to be fixed	Measures
Diet	Advice on the distribution of protein, beverage and calcium intake, and on reducing salt intake. - protein intake: 0.8g/kg/j (target of urinary urea around 5 mmol//kg/d) - salt intake: 4 – 6g/d (target: natriuresis < 100 mmol/d) - increasing alkalizing alimentation with elements with negative PRAL index (vegetables and fruits and alimentation plus elements rich in magnesium potassium and calcium 1000mg/d until 2000mg according to the needs according to the women cycle - try to prefer aliments with lower PRAL index and avoid very high PRAL index elements in the same meal to prevent an acidification too important

Resolubilize cystine in urine	- Dilute urine > 3L/d or even 3.5L/d to obtain a urine specific gravity <1005 on all urine even the morning - Nocturnal awakening around 2-3 a.m., do not remain without urinating for more than 3 hours during the day. - Optimal morning urine density < 1005 - Wake-up urine creatinine concentration < 5 to 8mmol/L according to the muscular mass
Alkalinize urine (urine pH between 7.5 and 8)	- Urine pH monitoring by voiding schedule to encourage self - Assessment: initially weekly then minimum monthly. Bring your "cystinuria" workshops with you - A diet, rich in vegetables, alkalinizing (low PRAL index negative ones if possible) - Dilution of one squeezed lemon in one liter of tap water to drink throughout the day. - Sodium bicarbonate capsules or a less salty water with a better PRAL index. - Potassium bicarbonate can be interesting but has to be very well managed. - if necessary introduce in plus potassium citrate diluted in the water and not in capsules for a better efficacy on the long term during all the nycthemer
Urinary tract infection	- Drinking plenty of fluids - Maintaining a urine pH less than 8 - Avoiding excessive personal hygiene. - Avoiding overweigh and constipation.
Pregnancy	No pregnancy without absolute proof of absence of calculus by a very low dose CT scan
Stress management	Encourage meditation ventral respiration cardiac coherence
Body composition and life style	Try to keep an balanced body composition with fat mass<30% and especially an abdominal perimeter under 88 cm to prevent the risk of urins acidification by induced insulinoresistance Enhance body movement to prevent sedentarity and its complications +++
Posturo therapy	Inverted postures ideally daily (yoga, pilates…)
Monitoring	- Continuous monitoring: a consultation every 3-4 months (excluding pregnancy). - Corn cure every 3 months in the event of lax prevention measures or reappearance of small stones (<2mm).

Table 1: Recurrence prevention [13].

Figure 1. The cystinuric woman's life cycle



Management of women with cystinuria throughout life

In addition to the standard treatment objectives of cystinuria (i.e., permanent dilution of urine, urine alkalinization with a pH range of 7.5 to 8.0, adjustment of dietary habits to control methionine and salt intake, increase in alkalizing foods [vegetables and fruit], and decrease in acidifying foods [meat, fish, eggs]), several particularities need to be taken into account during the life of a woman with cystinuria. Properly managed medical care, understood and accepted by the patient, helps prevent stone recurrence and their associated consequences.

Prenatal detection of a hyperechoic colon should prompt screening for cystinuria at birth, particularly in the female fetus [14] because they have a higher risk of UTIs due to their anatomy and increased cystine crystal-induced mucosal injuries. During infancy and childhood, girls are often exposed to cystitis [12]. Preventing the onset of UTIs is important in this population; therefore, promoting education on proper female intimate hygiene and fluid intake to avoid or limit the early risk of stone formation and UTIs is imperative. Repeated use of antibiotics can produce long-term deleterious effects to the intestinal microbiota and lead to intestinal hyperpermeability and weight gain, which, in turn, are factors that increase the risk of UTIs [15,16]. Daily life can be disrupted by the need to drink copious amounts of fluid throughout the day, which, consequently, causes frequent urination. Setting up individualized care plans in schools to promote healthy drinking habits can have a positive impact on children. Furthermore, maintaining hydration during the night may require a nasogastric or gastrostomy tube in infants, especially those with hypotonic-cystinuria syndrome. Similarly, it is crucial that young girls with cystinuria maintain an appropriate calcium intake to ensure they reach peak bone mass. Bone mass plays an important role during a woman's life and can be influenced by pregnancy, breastfeeding, and menopause. All these factors represent a risk for osteoporosis in young women with cystinuria. Potential Renal Acid Load (PRAL) is calculated using protein, phosphorus, potassium, magnesium, and calcium (PRAL index formula = 0.49 x protein (g/day) + 0.037 x phosphorus (mg/day) - 0.021 x potassium (mg/day) - 0.026 magnesium (mg/day) - 0.013 x calcium (mg/day)), and calcium deficiencies can contribute to a high acid load [17]. In other words, meeting the daily recommended calcium intake of 1000 mg—well distributed throughout the day—will help urine alkalinization and maintain an adequate pH above 7.5, preventing lithiasis recurrence [17].

Women of reproductive age

During the menarche period, young women suffering from

cystinuria will be advised to reduce protein intake due to the methionine content [13], exposing them to a vegetarian diet, which, if left unchecked, can lead to iron deficiency [18]. In young menstruating women, and even more so among vegetarians or vegans, it is important to assess the frequency and abundance of menstrual periods and regularly monitor iron levels, which is best corrected intravenously, since, in our experience, women who have a history of antibiotic treatment are particularly intolerant to oral iron supplementation (data unpublished).

The time of first sexual intercourse is also a risk. It is important to educate young women on the importance of emptying their bladder (which contains urine with alkaline pH) within 3 to 5 minutes after intercourse to limit the risk of urinary infection [19]. This immediate post-coital emptying of the bladder is, therefore, a habit worth adopting. General advice to avoid post-coital intimate hygiene with the use of soaps, suggesting it is harmful for the commensal local urethral and vaginal microbiota, is invaluable; proper hygiene practices will prevent damage to local commensal flora and protect against non-resident bacterial species, including *Escherichia coli*. It has been described that some women wash excessively in areas like the vulva, which can be deleterious for the local microbiota, especially vaginal and urinary, by modifying the pH of the vaginal mucosa. Additionally, it has been advised to not wash or fondle oneself, as the spermine contained in semen has an antibacterial effect in itself [19]. It is also recommended to wash or rinse in lukewarm water, without soap, dabbing (not rubbing) with a soft cloth in order to avoid mucous membrane irritation.

Similarly, estrogen-progestin contraceptives are not inadvisable per se, but it is important to remember that women with cystinuria are at risk of developing hypertension at a relatively early stage in life [20]. In cases of arterial hypertension, it is advisable to use continuous contraception, either without menstruation using an Intrauterine Device (IUD) or estrogen-free hormonal implant, or oral micronized progesterone, provided it is not complicated by repeated micro-bleeding and the saturation coefficient is maintained above 30%.

During the second phase of the menstrual cycle, certain women experience hotter conditions which can lead to insensible water loss; urine is more concentrated if the volume of fluid intake is not increased. Some women suffer from premenstrual symptoms complicated by water retention and depression, which can result in a tendency to not take in fluid regularly and, thus, an increase in concentrated urine.

We can, therefore, recommend the following to young women who need a feeling of freshness to use only water without soap because of the deleterious effects of biochemical products on the rectal, vulvar, and vaginal microbiota. These products are usually neutral, but mucosa and skin pH have to maintain acidic levels to preserve the quality of local commensal flora. Tampons can be used, as long as they are well placed in the vagina; sanitary towels are not recommended. The use of IUDs is not recommended, as it is associated with blood loss, increasing the risk of iron deficiency. The female condom is an alternate contraceptive when used correctly.

For the following reasons, we no longer use thiol-containing drugs to treat cystinuria. First, due to the potential deleterious complications of these drugs, we developed other efficient treatments without serious risks, like membranous glomerulopathy. Second, we have a multidisciplinary team of psychologists and dieticians to educate patients and provide a collective culinary workshop. Finally, our patients are educated to reach their goals in a variety of ways, like alkaline alimentation. Although we do not use thiol-containing drugs to treat patients with cystinuria [20], some nephologists use this treatment for brief periods; it is important to keep in mind the possibility of pregnancy when treating patients with thiol-containing drugs.

Before and during pregnancy

Before conception, it is advisable to check the stone-free status with a low-dose computed tomography scan and leave the eventual stone in place. It is important for women with hypertension to stop taking antihypertensive drugs, such as Angiotensin-Converting Enzyme (ACE) inhibitors or angiotensin II receptive blockers, as well as alkalizing supplements and thiol derivatives. Sodium and potassium bicarbonate should be used, as well as calcium for its alkalinizing effect, and iron levels should be assessed and deficits corrected. Bear in mind, there are many difficulties in managing the pain of renal colic. Ureteral stent insertion can cause discomfort and should be changed frequently due to hypercalciuria resulting from reduced secretion of parathyroid hormone-related protein by the mammary glands and placenta. The first trimester often poses problems like hydration and physical exhaustion. Medical providers should not hesitate to prescribe time off from work and, in case of nausea and vomiting, regular infusions. The second trimester is usually well tolerated. The third trimester has more risks, like limited hydration because the stomach is compressed by the uterus, acute pyelonephritis of the right kidney-especially if a ureteral stent is in place and premature delivery, often in emergency, due to dextrorotation of the uterus.

Abortions

Whether a woman opts for an abortion as a personal decision or for medical reasons, and regardless the term in which it is carried out, it is important to monitor cystinuric patients because the increased risk of iron deficiency can be associated with an increased incidence of infection, especially UTIs, and depression. It is important adequate psychological care is provided when needed.

Breastfeeding is possible for women with cystinuria; however, without time off from work and a strong support system, breastfeeding can present challenges because daily fluid intake ranges from 5 to 6 L to maintain hyperdiuresis. During this period,

a daily calcium intake of at least 2000 mg is recommended. Alkaline agents, like bicarbonate and citrate, can be used. In cases of hypertension, antihypertensive drug therapy should be adjusted to a drug deemed safe during lactation (methyldopa).

Menopause

Women with cystinuria are at risk of premature menopause, possibly associated with chromosomal abnormalities (unpublished personal case of mosaic Turner syndrome). If patients suffer from hot flashes, sustained hyperdiuresis, with a daily urine volume of at least 3 L, can be difficult to attain without significantly increasing fluid intake. It is important to monitor these women to ensure hyperdiuresis is maintained, even during sleep disturbance and hot flashes.

Miscellaneous

It is important to take into account the emotional burden experienced during pregnancy and after childbirth, as well as the guilt of disease transmission to one's child. In hypertensive women with cystinuria, medically assisted reproduction is problematic due to infectious and calculous recurrence, which can lead to miscarriage. Menometrorrhagia following miscarriage should not be overlooked; this may induce iron deficiency that is not regularly supplemented. Bone densitometry tests at menopause, or prior, should be conducted if calcium intake levels are low. Deficiencies in calcium can be supplemented with vitamin D daily rather than monthly.

In our experience, periureteral endometriosis is not uncommon and can simulate renal colic and stone migration. It is important to look for a cycle of pain that matches the menstrual cycle of the patient. In cases of endometriosis, the risk of iron deficiency is increased. Intravenous iron supplementation should be preferred when treating these patients due to their intolerance to oral iron.

Conclusion

We think it is helpful for clinicians to be aware of characteristics specific to female patients with cystinuria. Knowing these particularities will help educate young girls and women on the prevention of complications specific to their sex, like UTIs. It is also beneficial to look for possible differential diagnoses of renal colic, like endometriosis, and closely monitor pregnancies by ceasing the use of drugs incompatible with pregnancy (e.g., ACE inhibitors, thiol derivatives), adjusting alkalizing agents (e.g., bicarbonate and citrate), and ensuring stone-free status prior to conception. If these precautions are not taken, women with cystinuria can be exposed to severe maternal-fetal complications, such as sepsis with a urinary tract source, which can be complicated by premature delivery or even severe fetal distress. Understanding these characteristics will improve the prognosis of both renal function and overall survival, reduce the recurrence of renal colic and the need for radiation and antibiotics, and improve the quality of life in women with cystinuria.

In the future, we need more collaborations with the gynecologists, obstetricians and urologists to better describe and understand these cystinuric womens' specificities to improve the worsened prognosis of the female patient with cystinuria. Further studies need to be done in collaboration with these specific cystinurie female patient to prevent the evitable complications.

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