

Management of distal renal tubular acidosis (RTA) or RTA type I in pregnancy. Two case reports

Cristina Casanova¹, Ana Isabel Martínez¹, Jessica Subirá¹, Sergio Bea², Vicente Diago¹, Alfredo Perales¹, Jose Miguel Cruz²

¹ Obstetrics and Gynaecology Service

² Nephrology Service

University Hospital La Fe. Valencia, Spain.

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ABSTRACT

Distal Renal Tubular Acidosis (dRTA) or RTA Type I is a rare form of metabolic acidosis caused by a defect in urinary hydrogen ion excretion. We analysed pregnancy in two sisters with familiar RTA Type I and recessive autosomal inheritance associated with neurosensory deafness.

Haemodynamic changes in the kidney during pregnancy required treatment adjustment to prevent both obstetric and renal complications.

In neither case was maternal or foetal complications observed, and full-term babies were delivered vaginally without complications.

Key-Words:

Renal tubular acidosis (RTA); pregnancy; tubulopathies

INTRODUCTION

Renal Tubular Acidosis (RTA) is a clinical syndrome characterised by metabolic acidosis secondary to a disorder in renal acidification. The acidification may be manifested by a defect in the renal tubular reabsorption of bicarbonate and/or urinary excretion of hydrogen ion¹⁻³.

In terms of clinical and physiopathological aspects this disease can be classified into three groups: distal RTA or type I, proximal RTA or type II, and hyperkalaemic RTA or type IV^{2,4}.

Type I RTA, subject of this report, presents in two forms: the isolated form which is more frequently sporadic, although in some cases corresponds to an autosomal dominant inheritance, and the form associated to neurosensory deafness¹ (Butler-Albright disease) which is inherited as an autosomal recessive disorder⁵. RTA diagnosed in adults is usually acquired and it frequently presents in the context of autoimmune diseases. Moreover, there is also the so-called transient renal tubular acidosis or Lightwood syndrome secondary to the mechanisms of action of several toxicants (sulphonamide, mercury and mainly vitamin D)².

Distal RTA presents with an inappropriately high urine pH (>5.5) despite systemic metabolic acidosis coexisting. This is due to the fact that kidneys are unable to transport H⁺ from blood to the collecting tubules. In addition, urinary bicarbonate excretion is scarce (no more than 5% of the filtered quantity)².

The primary form (Butler-Albright disease) presents after the age of two years and in some cases it is already present in the first weeks of life, with vomiting, poliuria, dehydration and lack of weight gain^{3,6}.

Rickets can be observed if the condition goes untreated for many years. Moreover, another clinical manifestation is nephrocalcinosis (calcium phosphate calculi) due to hypercalciuria, alkaline urine and hypocitraturia which can be early detected by ultrasound scan. Muscular weakness can appear, and hypokalaemic flaccid paralysis episodes and rhabdomyolysis in pregnant women⁷ have been described. However, according to some authors, hypokalaemia is the most frequent electrolytic disorder in these patients⁸. The most common symptom in adults is renal lithiasis, either isolated or associated with nephrocalcinosis^{1,2}.

In these patients blood tests reveal normohypokalaemic and hyperchloraemic metabolic acidosis. Glomerular filtration is normal at the beginning but can decrease due to the renal impairment produced by nephrocalcinosis. Urinary pH is characteristically high (> 5.5) whereas titratable acid and ammonia excretions are decreased².

The process of distal urinary acidification determines the formation of an additional amount of bicarbonate, equivalent to the amount of secreted H⁺ ions towards tubular light as titratable acid and ammonium. Titratable acid represents the amount of H⁺ ions present in urine, combined with filtered buffer substances that are to be excreted, mainly monobasic phosphate (H₂PO₄). The other source of H⁺ ions present in urine are ammonia ions (NH₄⁺), resulting from excretion of H⁺ ions through the tubular cell and from the ammonium (NH₃) secreted from the cell.

In normal conditions urine is usually acid and its pH is lower than 6.5. The amount of free H⁺ ions in urine is quantitatively low because most of the H⁺ ions are secreted as titratable acidity and ammonium ion.

The urinary anion gap or urinary net charge (Na_o⁺ + K_o⁺ - Cl_o⁻), provides an estimate of renal ammonium

production (its excretion is usually accompanied by chloride) and differentiates RTA from bicarbonate digestive losses.

In dRTA, renal excretion of titratable acid and ammonium appear to be decreased. Decreased ammonium causes a positive urinary gap, since the urinary excretion of chloride appears to be also decreased: Na_o⁺ + K_o⁺ > Cl_o⁻.^{2,4,9}.

Diagnosis is based on the demonstration of normohypokalaemic and hyperchloraemic metabolic acidosis and a positive urinary anion gap^{2,5}.

The treatment consists mainly of bicarbonate (or citrate) administration to compensate for endogenous production of H⁺. Older children and adults usually require 1-3 mmol/kg/24h³.

The aim of this report is to analyse the possible maternal and foetal complications during pregnancy as well as the assessment of the newborn and the impact of pregnancy on the disease.

In the case of dRTA its uncommon presentation during pregnancy and its rarity in adults stands out. In terms of consequences to the foetus it is worth mentioning that persistent maternal acidosis can affect bone growth and development, and to a certain degree foetal distress, which can be prevented with adequate maternal acidosis management¹⁰.

■ CASE REPORTS

■ Case 1

A 28-year-old woman, with personal medical background of adverse reactions to aminoglycosides, was diagnosed with Distal Tubular Acidosis at the

Table 1

	NH ₄ ⁺	URINARY ANION GAP (mEq / l)	
Normal Conditions	Normal	Na _o ⁺ +K _o ⁺ > Cl _o ⁻	Positive +
RTA 1 and 4	Decreased	Na _o ⁺ +K _o ⁺ > Cl _o ⁻	Positive ++
Extrarenal Metabolic Acidosis	Increased	Na _o ⁺ +K _o ⁺ < Cl _o ⁻	Negative

age of 10 months as she presented delayed weight gain. This diagnosis was associated with bilateral neurosensory hypoacusia.

She gradually developed bilateral medullary nephrocalcinosis with no signs of lithiasis, nephritic colic, hypertension, hypercalciuria or proteinuria.

She had been treated since diagnosis with 5g/24h sodium bicarbonate, 5g/24h potassium bicarbonate and 30 mEq/24h potassium chloride. The electrolytic balance was normal, as was the glomerular filtration rate. At the age of 20, magnesium supplements were added, which she has required to date.

The patient became pregnant for the first time in June 2007, and presented normal plasma electrolyte levels. She maintained a correct electrolytic balance throughout pregnancy with stable creatinine clearance and continued the previous treatment (Table II).

She presented asymptomatic cortical lithiasis in the right kidney at week 22 of gestation which gradually disappeared during the puerperium.

Systolic and diastolic blood pressure were normal, ranging from 103-108 mm Hg and 64-67 mm Hg, respectively.

Ultrasound scans of the foetus were normal with satisfactory growth parameters and a good amniotic fluid index.

Her pregnancy ended in vaginal delivery at week 40. A male was born with a weight of 3040 g and an Apgar score of 9/10, with normal postnatal weight increases and no signs of hypoacusia.

To date, the patient's disease has not worsened as a result of her pregnancy, with good acid-based balance control and kidney function.

■ Case 2

A 26-year-old female (the sister of the previous case) with unremarkable personal medical background, but with a family background of Tubular Distal Acidosis (TDA), was diagnosed by a genetic study with TDA associated with bilateral neurosensory hypoacusia at 3 months of age, like her sister.

Subsequently, she also developed bilateral medullary nephrocalcinosis with no previous hypertension, proteinuria nor hypercalciuria. A satisfactory electrolytic control has been achieved since the diagnosis with supplements of 5g/24h sodium bicarbonate, 5g/24h potassium bicarbonate and 30 mEq/24h potassium chloride.

She became pregnant for the first time in January 2008, requiring increased potassium chloride, 60 mEq/24h, and additional magnesium supplements to normalise sodium, potassium and magnesium plasma levels from week 20 of gestation. She remained asymptomatic throughout the pregnancy with good kidney function, as shown by creatinine clearance within normal limits (Table III). No complications were observed during pregnancy, and systolic and diastolic blood pressure was normal, ranging from 120-138 mmHg and 60-72 mmHg, respectively.

Her pregnancy ended in vaginal delivery at week 40. A male was born with a weight of 3530g and an Apgar score of 9/10, and with adequate weight increases to date, presenting no signs of hypoacusia.

Table II

Blood test	Pre-pregnancy	During pregnancy
Na	140 mEq/l	136 mEq/l
K	4.1 mEq/l	3.7 mEq/l
Mg	1.8 mg/dl	1.69 mg/dl
Creatinine clearance	84 ml/min	84 ml/min
pH	7.26	7.36
PCO ₂	33.2 mmHg	19.8 mmHg
H ₂ CO ₃	19 mEq /l	35.4 mEq /l

Table III

	Pre-pregnancy	During pregnancy
Na	139 mEq/l	138 mEq/l
K	4.4 mEq/l	3.3-3.8 mEq/l
Mg	1.93 mg/dl	1.50-1.72 mg/dl
Creatinine clearance	104 ml/min	106 ml/min
pH	7.36	7.31
PCO ₂	36.2 mmHg	51.2 mmHg
H ₂ CO ₃	20.1 mEq /l	25.1 mEq /l

The patient continues to present a good acid-base balance control and kidney function, and the pregnancy did not affect her disease.

■ DISCUSSION

RTA has been reported in patients with various metabolic disorders, such as diabetic ketoacidosis, thyrotoxicosis with acute pancreatitis, alcoholic liver disease, and sickle cell disease, as well as in children with chronic hydronephrosis. It has also been described in a variety of conditions related to drugs, such as amphotericin B therapy for fungal infections, lithium for manic disorders, and dyazide for hypertension during pregnancy, as well as after toluene abuse^{2,10}.

We have found seven dRTA cases in pregnant women described in the literature: two with dRTA prepregnancy¹¹, four that onset during pregnancy with unknown aetiology^{7,12} and a case secondary to Sjögren's syndrome⁶. We did not find in the literature any case of pregnant women with renal tubular acidosis type I, of autosomal recessive inheritance and associated with neurosensorial deafness, as the cases here presented.

All the patients examined had a favourable evolution with an adequate control and treatment, and carried pregnancies to full-term delivering a healthy newborn vaginally^{7,10,11}. However, one case presented risk of preterm delivery at week 27 that was delayed with tocolytic drugs. Pregnancy ended in caesarean section at week 36 due to suspicion of loss of foetal wellbeing evidenced by cardiotocography. A newborn was delivered with birth weight appropriate for gestational age and with normal neonatal development and growth¹². In the cases presented here, both patients carried pregnancies to full-term delivering vaginally and did not present risk of preterm delivery. Some authors state that if tocolytic drugs are required in patients with RTA, beta-adrenergic blocking drugs must be avoided since they can aggravate the pre-existing hypokalaemia, as they produce hyperglycaemia and subsequently a transient hypokalaemia. If renal function is not affected, the tocolytic agent chosen would be magnesium sulphate¹⁰.

As dRTA is a rare disorder uncommonly encountered in pregnancy and adults no treatment and follow-up guidelines have been clearly established⁷.

A close follow-up during pregnancy by both the obstetrician (early detection of foetal anomalies) and nephrologist (strict control of acidosis, electrolyte balance, and blood pressure) is essential in patients with dRTA due to the changes undergone by the mother during pregnancy:

- a) Renal haemodynamic changes: Physiological hypervolaemia with a greater tendency towards developing pregnancy-induced hypertension (PIH), especially during the first trimester¹¹ that returns to normal after delivery.
- b) Ionic changes: Plasma levels of calcium and magnesium decrease, as well as maternal plasma potassium concentration that decreases 0.5 mEq/l during mid-term pregnancy. It is essential to check potassium levels in these patients since prolonged vomiting in pregnant women leads to hypokalaemia and metabolic alkalosis.
- c) Acid-base balance: Chronic maternal acidosis may lead to foetal growth delay and foetal distress¹⁰.

Glomerular filtration rate is increased during pregnancy by about 50%, increasing also the filtered load and the creatinine clearance¹⁰. Therefore, it is not surprising that to maintain a satisfactory electrolytic control during pregnancy the treatment had to be modified in both cases by increasing potassium chloride and adding magnesium supplements in one of the cases. By following this treatment neither patient experienced symptoms of hypokalaemia such as muscle weakness.

The only maternal complication observed during pregnancy was cortical lithiasis in the right kidney that disappeared during the puerperium.

Blood pressure control was normal in both cases with systolic and diastolic ranges of 110-130 and 60-80, respectively.

Foetal growth was adequate during pregnancy as well as the newborn weight (P₅₀).

Adequate management of renal pathology and acid-base balance means the disease does not determine the mode and time of delivery; these aspects depend only on obstetric causes. Here no problems or complications were observed with vaginal delivery.

Pregnancy, unless complications occur, does not affect either the future prognosis of maternal renal disease. In fact, in cases where renal tubular acidosis appeared during pregnancy, the patient completely recovered after delivery¹².

Since RTA is an autosomal-recessive inherited disease both patients had genetic counseling¹. The parents and the two brothers did not present any clinical manifestations of the disease. They were informed therefore that the only risk of disease in descendants was if their husbands were carriers, a very remote probability.

In summary, RTA is a very uncommon disorder during pregnancy. With delayed diagnosis and treatment the disease evolves towards renal failure as a consequence of nephrocalcinosis; however excellent prognosis is associated with early diagnosis and treatment^{2,3}. This is easier when the disease onsets in early infancy since it is of genetic origin, as in our cases. Joint and multidisciplinary management of these patients by the obstetrician and nephrologist is vital to reduce the maternal-foetal risks that can arise from this pathology. A correct management ensures a normal foetal development and a minimal risk for the mother, as it can be observed in the cases herein presented as well as in those described in the literature.

Conflict of interest statement. None declared.

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Correspondence to:

Dr Cristina Casanova
Obstetrics and Gynaecology Service
University Hospital La Fe
Av. Campanar, 21. Valencia, Spain
casanovapedraz@hotmail.com