CASE REPORT

Outpatient management of Gitelman's syndrome in pregnancy

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SUMMARY

Gitelman's syndrome is a congenital renal tubular defect which affects the apical membrane of the distal convoluted tubule of the renal system. The syndrome is characterised by hypokalaemia, hypomagnesaemia, metabolic alkalosis and hypocalcuria. There are only a few cases describing the impact of Gitelman's syndrome on pregnancy and the foetus. Although most pregnancies have favourable outcomes, fetal demise has been reported in the third trimester. We report the successful outcome of pregnancy in a patient with Gitelman's syndrome who continued on amiloride in pregnancy to optimise potassium and magnesium levels and review the literature for pregnancy outcomes of this condition.

BACKGROUND

Gitelman's syndrome (GS) is a renal disorder that can cause exacerbation of electrolyte disturbances in pregnancy. Most patients have good obstetric and neonatal outcome despite ongoing hypokalaemia and hypomagnesaemia. Nevertheless, these women and their healthcareers should be aware of the potential complications of GS and the need for careful electrolyte monitoring and the increased need for potassium and magnesium supplementation in pregnancy.

CASE PRESENTATION

An 18-year-old woman with GS was referred to our joint obstetric renal antenatal clinic in her first pregnancy. She booked at 10 weeks. At her booking visit, she was on oral supplements of magnesium 4 mmol (194 mg) three times a day and amiloride 15 mg twice a day. Physical examination and cardiovascular measurements were normal. She was generally well apart from mild hyperemesis in the first trimester. Initial biochemistry revealed normal serum potassium (3.6 mmol/l; normal range 3.5–5.0 mmol/l) and magnesium levels (0.6 mmol/l; normal 0.6–1.0 mmol/l).

The patient's medications were changed from amiloride to spironolactone owing to the limited information of effects of amiloride on fetal development as compared with spironolactone.¹ By the 14th week of gestation, serum magnesium had fallen to 0.46 mmol/l. After a multidisciplinary meeting, it was decided to restart amiloride and stop spironolactone. The magnesium supplements were also increased to 8 mmol three times a day. There was an immediate improvement in the serum magnesium levels (0.59 mmol/l) (figure 1).

The patient remained generally symptom-free with borderline serum magnesium and normal serum potassium levels until the 17th week of gestation. The potassium levels decreased to 2.6 mmol/l and the magnesium to 0.5 mmol/l. Potassium chloride supplementation was started and magnesium supplementation was increased to 12 mmol three times a day. Monitoring of bloods weekly continued until delivery as an outpatient. By the 23rd week of gestation, owing to persistently low serum magnesium levels, the Mg supplements were increased to 16 mmol three times a day. Fortnightly growth scans revealed a normal size baby with normal liquor and Dopplers. At 34 weeks, there was a slight decrease in abdominal circumference, but the liquor volume and Dopplers were maintained. The serum magnesium levels remained stable at 0.66 mmol/l and potassium levels at 3.6 mmol/l.

An elective induction of labour was planned for 37 weeks. The patient had an uneventful spontaneous vaginal delivery of a male infant weighing 2720 g (40th centile on customised growth chart). Postnatally, the patient remained well. She was discharged back to the renal team on magnesium supplements and amiloride 20 mg twice a day.

DIFFERENTIAL DIAGNOSIS

Bartter syndrome is the major genetic syndrome to consider in the differential diagnosis of GS. In GS, the site of defect is the distal convoluted tubule, whereas in Bartter's, the thick ascending loop of Henle is affected. The biochemical features of both conditions include hypokalaemia and activation of the renin-angiotensin-aldosterone axis.² GS is milder in symptoms and presents around adolescence with hypocalcuria. Bartter's, on the other hand, presents earlier in childhood with more severe symptoms and hypercalcuria.^{3 4} Other acquired conditions with renal hypomagnesaemia to differentiate with GS are diuretic and laxative abuse and chronic vomiting.

TREATMENT

Pregnant women with GS should be managed under a multidisciplinary team involving an obstetrician and a renal physician in conjunction with a specialist midwife. Management of women with GS should ideally begin prior to pregnancy to allow time for appropriate counselling regarding the potential difficulty of optimising electrolytes in pregnancy and the side effects of exacerbation of hypomagnesaemia and hypokalaemia such as ventricular arrhythmia. The demands of frequent antenatal visits and blood tests should not be underestimated.

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GH Mg and K levels in pregnancy

Figure 1 The patient's magnesium and potassium levels in pregnancy.

Most patients with GS need magnesium and potassium supplementation in pregnancy (see online supplementary table S1). While oral supplementation of magnesium and potassium was adequate in our patient, half of the reported cases needed intravenous supplementation which was started due to exacerbation of symptoms and/or continuing deterioration of serum levels.^{5–10}

In addition to electrolyte supplementation, aldosterone antagonists such as spironolactone, amiloride and eplerenone have been used successfully in pregnant women with GS.⁶ Spironolactone has well-recognised antiandrogenic adverse effects. Despite this, there are no specific birth defects in neonates or feminisation of male babies born to mothers taking this drug.¹¹ Studies on rats have shown feminisation of the genitalia in the male offspring of rats treated with spironolactone during late pregnancy in doses five times greater than those used in humans. Also, hypoprolactinaemia and reduced weights of accessory sex organs have been reported in adult female rats born to mothers that had been treated during pregnancy with spironolactone in doses 2.5 times those used in humans.¹² Morton *et al*¹³ reported the use of eplerenone in a pregnant patient with GS owing to her intolerance to magnesium and potassium supplements because of nausea, and amiloride because of tinnitus.

Women with GS need to see an anaesthetist antenatally owing to the risk of perioperative disorders associated with hypokalaemia or hypomagnesaemia, for example, laryngeal spasm, stridor, paraesthesia, tetany, convulsions, coma and ventricular arrhythmia. These women require a detailed preoperative assessment with optimisation and serial monitoring of electrolyte levels, baseline ECG for QT interval length (as in 50% of GS cases, the QT interval is prolonged).

DISCUSSION

GS was first described in 1966 as a familial disorder characterised by hypokalaemia and hypomagnesaemia.¹⁴ It results from congenital defects in the renal tubular handling of sodium, potassium and chloride.¹⁵ Patients present with fatigue, dizziness, muscle weakness and cramps.

The prevalence of GS is about 1 : 40 000 with a heterozygote prevalence of approximately 1%; making it one of the most frequent inheritable renal tubule disease.³

GS is caused by inactivating mutations in the gene SLC12A3; which encodes for the thiazide-sensitive sodium chloride transporter (NCCT). NCCT is located in the distal convoluted

tubule of the kidney, a segment known to play an important role in the reabsorption of magnesium in the nephron.¹⁶

GS is an autosomal-recessive condition and therefore the recurrence risk for parents with an affected child is 25%. Patients with GS have a low risk of having children with GS (1/400) unless the couples are consanguineous.³ Invasive antenatal investigations are not advised as the long-term prognosis for GS is good.

In pregnancy, owing to the expansion of extracellular space and increased renal clearance, magnesium levels decline through gestation. Magnesium is vital for many biochemical processes and its regulation depends on renal excretion. In GS, there is a disruption of sodium chloride reabsorption in the distal convoluted tubule. This causes vascular volume contraction leading to activation of the renin–angiotensin–aldosterone axis. The elevated aldosterone leads to increased Na⁺ reabsorption which results in increased secretion of potassium and hydrogen ions, resulting in hypokalaemia and metabolic alkalosis.

Normalisation of serum magnesium and potassium levels in pregnancy as seen in all reported cases is difficult to achieve.^{5–10 13 17–20} In spite of this, the majority of the cases report uncomplicated maternal and fetal outcomes. In the reported pregnant cases with GS, there has been only one case of stillbirth reported by Lakhi *et al*⁸ where fetal demise occurred at 28 weeks with a K⁺ of 2.3 mmol/l in an asymptomatic patient. However, in rodent models it has been shown that a dietary-induced maternal hypomagnesaemia during gestation was associated with an increased miscarriage rate, increased incidence of periventricular haemorrhage and decreased birth weight.²¹ Also, one-third of the reported cases have described oligohydramnios as a complication of GS.^{5–9}

Although the metabolism of magnesium and potassium are closely linked, Betinelli *et al*²² demonstrated that in GS; magnesium supplementation fails to completely restore magnesium depletion and extracellular and intracellular potassium levels.

Learning points

- ▶ Gitelman's syndrome (GS) is a renal disorder that can cause exacerbation of electrolyte disturbances in pregnancy.
- ▶ Most patients have good obstetric and neonatal outcome despite ongoing hypokalaemia and hypomagnesaemia.
- ▶ Most patients with GS need magnesium and potassium supplementation in pregnancy.
- ▶ Pregnant patients with GS need careful electrolyte monitoring in pregnancy and should be managed under a multidisciplinary team involving obstetricians, specialist midwives, renal physicians and anaesthetists.

Competing interests None.

Patient consent Obtained.

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