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Gitelman syndrome during pregnancy – from diagnosis to treatment: a case series and review of the literature

Abstract

Objective: Gitelman syndrome (GS) is a rare renal disease, originating from a defect in the Na-Cl co-transporter in the distal tubule, which causes hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis and low-normal blood pressure. Mild hypokalemia of pregnancy is physiological. Fatigue, nausea, vomiting, polyuria and low blood pressures are also common complaints associated with a normal pregnancy. Therefore, the diagnosis of an organic renal disorder, i.e., GS, may go undetected, until severe hypokalemia and possible life-threatening cardiac arrhythmias develop. Maternal consequences are obvious. The possibility of fetal pathology remains unclear.

Study design: In this study, we describe nine pregnancies in seven women with a clinical diagnosis of GS. Nearly all women were diagnosed initially during pregnancy. We describe their clinical presentation, serum and urine electrolyte levels during pregnancy and immediately post-partum, their treatment and pregnancy outcome.

Results: Fetal pregnancy outcomes were mostly favorable. While it is likely that women suffering from GS do not require special fetal surveillance, they are at high risk for electrolyte depletion and thus aggravation of GS during pregnancy.

Conclusion: Clinical suspicion of GS should arise in all women presenting with symptomatic hypokalemia. Once the diagnosis is made, adequate supplementation and routine maternal monitoring should ensue.

Keywords: Gitelman syndrome (GS); pregnancy; renal.

Introduction

Gitelman syndrome (GS) is an autosomal recessive syndrome, first described in 1966 [12]. It is characterized by hypokalemia, hypomagnesemia, hypocalciuria and metabolic alkalosis. People suffering from this syndrome present with secondary hyperreninism-hyperaldosteronism and thus maintain normal to low blood pressure [15, 19]. The reported incidence is 1 in 50,000 people.

The pathologic defect is related to mutations in the renal thiazide-sensitive sodium chloride co-transporter (NCCT) located in the distal tubule. The mutation is located in the SLC12A3 gene on chromosome 16 [14].

Patients are usually asymptomatic or present with muscle cramps, fatigue, tetany, nausea, vomiting, polyuria, nocturia and prolonged QT syndrome. Diagnosis is typically established during adolescence or early adulthood.

Several physiological adaptations occur during normal pregnancy. There is volume expansion in addition to an increase in both renal blood flow and glomerular filtration rate. An increase in tubular reabsorption maintains electrolyte balance [7]. Increased progesterone secretion causes an anti-mineralocorticoid effect, and, therefore, the net effect is a balance in potassium concentration, most of which supplies the growing fetus [3, 11].

Common causes of hypokalemia during pregnancy are dilution, increased fetal demands [9], diarrhea and hyperemesis gravidarum. An infrequent but important cause is GS.

Case reports

Between 2006 and 2012, seven women with hypokalemia and suspected GS were followed at our high-risk pregnancy unit. These women had a total of nine pregnancies, all complicated by clinical GS. We reviewed the course of these pregnancies from the time of diagnosis until delivery and shortly thereafter in the postpartum period. We
collected data on the age and parity of the women, gestational age at the time of diagnosis, presenting symptoms, treatment type during pregnancy, serum and urine electrolyte concentrations at their nadir and under supplemental treatment, kidney function, maternal and fetal complications and outcome, gestational age at delivery, method of delivery and baby’s weight. These data are presented in Tables 1 and 2.

The mean age at diagnosis was 31 years. All but one woman were diagnosed in the second or early third trimester, with symptoms of volume depletion including weakness, dizziness, pre-syncope and diarrhea (which in itself could have aggravated further potassium loss). Two women were discovered by chance, after having been admitted to the hospital due to unrelated symptoms of premature contractions and elevated hepatocellular enzymes. All patients denied use of diuretics.

The mean age of diagnosis was at 28 weeks of gestation, with a median of 24 weeks. Nearly all women were diagnosed during their first pregnancy, apart from one woman, who had been diagnosed prior to her first pregnancy, and one woman, who had had an uneventful first pregnancy, but two consecutive symptomatic pregnancies.

The mean serum potassium level at diagnosis was 2.65 mEq/L (range 2.19–3.2 mEq/L). The mean serum magnesium level at diagnosis was 1.6 mEq/L (range 1.4–1.96 mEq/L). Blood pressure was mostly within the low-normal range, with a mean of 107/67. One of the signs of GS is hypocalciuria. However, urine calcium levels were obtained in only one patient and were very low (11 mg/day; see Table 1 patient 4).

Renal function was preserved in nearly all women, as demonstrated by their creatinine clearance. All but one woman, i.e., six women during seven pregnancies, required repeated potassium and magnesium supplementation. In most patients, intravenous supplementation was administered together with oral KCl and magnesium Diasporal tablets (containing magnesium citrate). Under this intensive replacement therapy, serum potassium and magnesium levels rose, but remained in the low to low-normal range (mean 3.44 and 1.7 mEq/L, respectively).

Pregnancy outcomes varied between the women, and included normal uncomplicated gestations (n=4), intrahepatic cholestasis of pregnancy (ICP, n=2), intra-uterine growth retardation (n=1), preeclampsia (PE, n=1) and shortening of the uterine cervix (n=1). Most women (n=6) delivered vaginally, while two had cesarean sections due to obstetrical indications (worsening of preeclampsia and breech presentation). Most women delivered at or near...
term (37 weeks on average). Induction near term was performed due to obstetrical reasons unrelated to GS (ICP, PE). No fetal complications were observed. The weights of all newborns were appropriate for gestational age. Potassium levels obtained within 24 h postpartum normalized without supplementation in all but two patients, who had near-normal levels (3.42 and 3.46 mEq/L, respectively).

**Comment**

The tubular defect in GS is almost identical to that seen with chronic ingestion of a thiazide diuretic. Impaired sodium chloride reabsorption leads to mild volume depletion and activation of the renin-angiotensin-aldosterone (RAAS) axis. The combination of secondary hyperaldosteronism and increased distal flow and sodium delivery enhances potassium and hydrogen secretion at the secretory sites in the connecting tubules and collecting tubules, leading to hypokalemia and metabolic alkalosis. Patients with GS have a lower blood pressure than that seen in the general population. The diagnosis of GS is largely one of exclusion, made in patients who present with unexplained hypokalemia and metabolic alkalosis with a normal or low blood pressure, and in whom other etiologies are ruled out. Of note, Bartter’s syndrome, a closely associated disorder also consisting of hypokalemia, alkalosis and normal to low blood pressures, can be differentiated from GS, since it is usually diagnosed earlier (with its two common subtypes, neonatal and classical, appearing in later childhood) and is more severe (complicated by vomiting, failure to thrive and end-stage renal disease if left untreated).

During pregnancy, the activity of all components of RAAS is increased, especially by the third trimester, further contributing to hypokalemia. A thorough review of the literature reveals few reports about the impact of GS on pregnancy. Of these, Basu et al. [2] reported the outcome of three successive pregnancies in a patient with GS, associated with difficulties in achieving physiological potassium and magnesium levels throughout gestations. Jones and Dorrell [13] reported a 35-year-old patient with suspected GS who had two successful outcomes after two miscarriages. Both pregnancies were associated with oligohydramnios [13]. In a cohort study of 50 patients with GS, 20 of whom gave birth, seven had had complicated pregnancies. These complications included dehydration, the need for intravenous potassium and/or magnesium administration, severe cramping, Sheehan’s syndrome, gestational diabetes, miscarriages in the first trimester,
premature delivery, polyhydramnios, preeclampsia and placental abruption. Other than fluid deficit and electrolyte imbalances, it remains unclear whether any of these complications were related to GS [5]. Mascetti et al. described five patients with GS. Pregnancy was uneventful in four of them but was complicated by fatigue and tetanic seizures in the remaining one [17]. Finally, a recent review by Calò and Caielli [4] reports possible cardiac abnormalities in patients with GS; reduction of myocardial perfusion, myocardial contractile recruitment and cardiac index; and increased production of nitric oxide, which, at times of increased demand, such as pregnancy, may lead to arrhythmias and sudden cardiac death.

While there are no reports of mortality or morbidity in the offspring of maternal GS, and no adverse fetal outcomes directly related to GS have been reported, animal models with gestational hypomagnesemia demonstrate increased incidence of periventricular hemorrhages [1, 6, 8–10, 17, 20, 21].

In our case series, all but one patient were diagnosed during pregnancy due to common pregnancy symptoms, such as hyperemesis, weakness and fatigue. These complaints are generally regarded as physiological during pregnancy and, therefore, may be dismissed by both the patient and the physician. It is possible that our patients were only diagnosed at later stages of their pregnancy, since in the first and early second trimester such reports went unnoticed and uninvestigated. Moreover, excretion of magnesium and potassium during pregnancy is greatest during the second trimester [18]. In all nine pregnancies, the patients required repeated treatment with supplemental intravenous potassium and magnesium. In addition, two patients required supplemental potassium chloride oral syrup and six were discharged with potassium chloride extended-release tablets (SLOW-K, potassium chloride tablet, extended release, Novartis Pharmaceuticals Corporation, Basel, Switzerland). Magnesium Diasporal tablets were provided to five patients exhibiting persistently low serum levels of magnesium despite intravenous supplementation. Patients were discharged from the hospital with a recommendation to maintain potassium and magnesium within low-normal level by oral potassium (potassium chloride extended-release, Qualitest Pharmaceuticals, Huntsville, AL) and Magnesium diasporal (Doetsch Grether, Basel, Switzerland), if necessary. As is evident from Table 2, despite supplement treatment, the serum potassium and magnesium levels reached were within the low-normal range. Under this treatment patients were asymptomatic. It should be noted that one patient diagnosed with prolonged QT syndrome during early adulthood, who had had an implantable cardioverter defibrillator prior to pregnancy, was especially difficult to treat. Despite massive supplementation, she continued to exhibit low serum potassium levels, but did not require activation of the defibrillator.

As for fetal outcome, no adverse outcomes directly related to GS were noted. Despite a possible association between GS and oligohydramnios mentioned in the literature, all nine pregnancies had normal amniotic fluid indexes throughout gestation [9, 13].

It appears that the main challenge during pregnancy is maintaining normal serum potassium and magnesium levels. However, our experience shows that normalization of these electrolytes is not necessary for successful perinatal and maternal outcomes. These results are compatible with previous findings by Talulikar and Falk [21]. Moreover, we observed that major fluctuations in serum potassium and magnesium levels are possible during consecutive gestations, so that GS may be diagnosed in women with a history of a previous uneventful pregnancy and the characteristic electrolyte abnormalities may not recur in all gestations. This finding is compatible with a previous report by Kwan and Falk [16] and may reflect a better physiological adaptation to renal changes in pregnancy.

The limitation of this report is that the diagnosis of GS in our patients was clinical and not genetic. Today, there are genetic tests available for the diagnosis of GS through common mutations in the thiazide-sensitive NaCl co-transporter. Yet the accepted diagnosis is one of exclusion and routinely clinical, based on symptoms and biochemical abnormalities.

In conclusion, general obstetricians should be aware of the possible diagnosis of GS in pregnant women exhibiting hypokalemia and hypomagnesemia and should monitor and treat their electrolyte levels accordingly. Treatment should aim to achieve low-near normal, and not necessarily normal, serum electrolyte concentrations. The treatment is probably mainly required to maintain maternal well-being, as no adverse fetal outcomes clearly related to GS have been documented.

Conflict of interest statement

Conflict of interest: The authors report no conflict of interest.

Ethics statement: Institutional review board approval was obtained for this research. Due to the retrospective and descriptive nature of our analysis, Helsinki approval was deemed unnecessary.

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