Use of Potassium-Sparing Diuretics for Serum Electrolyte Management in Pregnant Patients with Gitelman’s Syndrome

Gurjaspreet K. Bhattal*, Andrew Keller, Sabrina Ghim and Rahim F. Ismail
University of Central Florida, USA

Abstract

Gitelman’s syndrome is a rare disorder affecting the NCCT transporter in the distal convoluted tubule, seen in about 1 in 40,000 individuals. Although a relatively benign condition otherwise, it tends to manifest with persistent hypokalemia and hypomagnesemia during pregnancy and can have multiple clinical manifestations ranging from mild nausea, vomiting, and muscle cramping to seizures and prolonged QT intervals. A total of 27 cases of pregnant females with Gitelman’s syndrome have been reported in the literature thus far and most of them have resulted in favorable outcomes regardless of the intervention used. While oral and/or IV supplementation is considered a must for managing hypokalemia and hypomagnesemia during pregnancy, no guidelines have been established regarding the use of potassium-sparing diuretics for the same. We reviewed the 27 case reports with 33 pregnancies in 8 of which, potassium-sparing diuretics (spironolactone, amiloride, and eplerenone) were used in conjunction with oral and/or IV supplementation. Our review found that adding diuretics to the regimen results in better symptom control and lower rates of premature births, fetal demise, and gestational complications without compromising the birth weights of the neonate, or the levels of serum potassium and magnesium levels attained during the pregnancies. Additionally, the feared complications of feminization of the male fetus or teratogenic effects of other potassium-sparing diuretics were not seen in any of these cases. However, establishing guidelines and assessing the long-term safety profile of using potassium-sparing diuretics during pregnancy for patients with Gitelman’s syndrome warrants a randomized control trial.

ABBREVIATIONS

NCCT: Na-Cl-Co-Transporter; IV: Intravenous; C/S: Cesarean-Section; GDM: Gestational Diabetes Mellitus; IUGR: Intra-Uterine Growth Restriction

INTRODUCTION

Gitelman’s syndrome is a relatively uncommon disease state that has been estimated to affect about 1 in 40,000 individuals [1]. It is often diagnosed in childhood [2] and caused by a defect in the SLC12A3 gene which has an adverse impact on the NCCT transporter, a transporter critical for renal electrolyte homeostasis. The NCCT transport is a key player in sodium reabsorption and regulation in the distal tubule and is commonly utilized in drug therapy. Gitelman’s syndrome has a diverse range of clinical manifestations including: extremity cramping, fatigue, polyuria and nocturia, chondrocalcinosis, growth retardation, later onset hypertension, and potassium wasting in females [3].

While Gitelman’s syndrome was recognized as a separate disorder than Bartter’s syndrome as early as 1966, an understanding of treating these patients during pregnancy is relatively limited. Physiological changes in electrolyte status occur in pregnancy regardless of renal compromise. Studies show that some women have a decrease in serum calcium during pregnancy [4]. Hypomagnesemia after 33 weeks has been reported as well [5]. Various interventions such as oral electrolyte replacement, IV electrolyte replacement, amiloride, spironolactone, eplerenone and a combination of the above medications have been noted to be effective in the literature. To the knowledge of the authors of this review, 2009 was the earliest reported case of use of potassium sparing diuretics in pregnancy complicated by Gitelman’s syndrome [6]. Prior to this, only electrolyte supplementation was reported. In this review, we will analyze the relatively recent use of potassium sparing diuretics vs. electrolyte replacement for management of hypokalemia in pregnancy in a patient with Gitelman’s syndrome.

Literature Review

We present a review of interventions, maternal and fetal impact, and final outcomes of 33 pregnancies reported in literature in 27 patients diagnosed with Gitelman’s syndrome.

Diagnosis

10 of the 27 patients had genetically confirmed mutations in
the SLC12A3 gene (Table 1(included as supplementary)). Of the 10 patients, one patient had a missense mutation, one had a non-activating mutation, and five had inactivating mutations [6-11].

20 of the 27 patients had been diagnosed either in a non-pregnant state or in a prior pregnancy. Some of the common presenting symptoms at the time of their diagnosis were proximal muscle weakness, fatigue, paresthesias, and development of muscle pain and weakness following exercise. Of the 20 pre-diagnosed patients, 3 patients used potassium-sparing diuretics including spironolactone, and eplerenone before pregnancy. Two of those patients continued use during pregnancy and delivered healthy infants without any complications [6,7]. One of those three patients did not continue her spironolactone use into pregnancy. She gave birth at 34 weeks via a C/S and the infant remained in the NICU for 14 days until lung maturation was achieved and was later discharged in good condition [12]. Another patient was using an oral contraceptive containing Drosperrine prior to her 1st pregnancy but did not use any potassium-sparing diuretics during her pregnancy. Unfortunately, her first pregnancy resulted in fetal demise at 7 weeks and 6 days [13].

Clinical Condition

The clinical condition of the patients varied from asymptomatic to mild nausea or vomiting to recurrent seizures and a need for cardioversion. A majority of the patients presented with mild symptoms of nausea, vomiting, muscle cramps, fatigue, and paresthesias. Five patients remained asymptomatic throughout pregnancy despite having hypokalemia and hypomagnesemia (Table 1(included as supplementary)). Most of the patients who were asymptomatic or had mild symptoms delivered healthy babies without any complications. Slight decrease in fetal abdominal circumference at 34 weeks was noted on one of the pregnancies in a patient with mild symptoms but no other complications were observed [14].

Among the more severe symptoms were diffuse muscle paralyses, seizures, dizziness, syncope, prolonged QT with Ventricular tachycardia. Seizures were noted in three cases [14-16]. In the first case, the patient had a history of two spontaneous abortions at weeks 5 and 9 of gestation [15]. She presented with new onset seizures after weakness and syncope lasting 6 weeks. At 37 weeks, she was found to have oligohydranmios. Labor was induced at 37 weeks and she delivered a healthy infant vaginally without any complications. The second case reported a patient that presented with fatigue and tetanic seizures [16]. She delivered a healthy infant with no complications at 38 weeks. In the third case, the patient presented with profound muscle weakness and had seizure-like activity during admission with prolonged QT, V-tach following a second seizure, hypotension, and asystole [14]. She was cardioverted twice, returned to sinus rhythm, and remained in the hospital for 14 days. She was induced for post-term pregnancy at 41 weeks and delivered a healthy infant without complications. In another report, a patient presented with diffuse muscle paralysis and underwent a C-section at 34 weeks, delivering an infant who stayed in the NICU for 14 days and was discharged without complications. She had a history of pre-pregnancy ED admissions with respiratory arrest and muscle paralysis [12].

Fetal demise was reported in two cases [13,17]. In the first case, the patient initially presented with mild symptoms of gastroenteritis and vomiting but at 28 weeks, she was found to have oligohydranmios with no fetal heart activity. She presented at gestational week 24+ with potassium of 2.5 mmol/L and magnesium of 1.0 mmol/L. She endured an adverse fetal outcome despite IV and oral K+ and Mg2+ supplementation. The infant was stillborn and was found to have a normal autopsy and karyotype. Postpartum, she developed paresthesias and muscle weakness [17]. In the second case, the patient presented with K+ of 2.9 mmol/L and Mg2+ of 1.4 mmol/L and was given oral potassium and magnesium supplementation but endured fetal demise at 7 weeks and 6 days. Her serum K+ and Mg2+ levels at this time were 3.6 mmol/L and 1.4 mmol/L [13].

Of the cases reviewed, gestational diabetes was reported in three patients [18-20]. Two of these were controlled with diet while one case required insulin. Amiloride was used in one of these patients and the baby developed macrosomia [20]. However, the baby was delivered via a C/S under general anesthesia and no post-op complications were noted. In one of the other cases, the patient presented with fatigue, muscle weakness, and hyperemesis and developed gestational diabetes along with oligohydranmios. She was treated with insulin and underwent a C-section to deliver a healthy infant without any complications. In the third case of GDM, the patient underwent an uncomplicated pregnancy with elective C-section at 39 weeks, delivering a healthy infant without any complications. Of note, she was severely hypokalemic during her first pregnancy and required IV supplementation of potassium and magnesium. She received oral supplementations during her second pregnancy.

Two patients had a history of prior spontaneous abortions [13,15]. The first patient had had 2 spontaneous abortions previously and had a normal fetal outcome despite having oligohydranmios in the current pregnancy. However, the other patient had had 3 prior spontaneous abortions and a fetal demise at 23 weeks of gestation. In the current pregnancy, her fetus was found to have severe IUGR with reversed end-diastolic placental flow. She gave birth to a very low birth weight, viable infant, 636 g at 28 weeks of gestation via a C/S [13].

The most common symptom reported among the eight patients who used potassium-sparing diuretics during pregnancy was mild hyperemesis (Table 1(included as supplementary)). While two patients remained completely asymptomatic despite persistent hypokalemia, one patient required 39 admissions for IV infusions antenatally [21]. Some other symptoms seen among these patients were limb paresthesias and cramps. No fetal deaths or severe symptoms such as seizures, dizziness, syncope, or QT-prolongation were reported in this group. Oligohydranmios was reported on one patient [6] while GDM and macrosomia [20] was reported in another but the fetal outcome was perfectly normal and the deliveries were via planned C-sections without any complications.

Of all the cases reviewed, a majority of patients had symptoms at presentation, but underwent successful induced or spontaneous deliveries or C-sections to healthy infants without any complications. There were six cases that presented with oligohydranmios, one of which presented additionally with
partial placenta Previa and IUGR [9]. IUGR along with reversed end-diastolic placental flow was seen in another patient already mentioned above [13]. Healthy infants were delivered in 4 of these 6 cases with oligohydramnios. There was one case of a stillborn infant, one case of fetal demise, and one infant that had a 14-day NICU stay for respiratory maturation issues.

**Intervention**

Various interventions were used to correct the potassium and magnesium levels during pregnancy. Of the 33 pregnancies, IV or oral potassium and/or magnesium replacement was given during 29 pregnancies. Additionally, of the 32 pregnancies observed, potassium sparing diuretics (amiloride, eplerenone, or spironolactone) were used in conjunction with potassium and magnesium supplementation in 8 of the pregnancies. No intervention or alternative medicine (homeopathy) was used in 3 pregnancies (Table 1 (included as supplementary)). The first patient in the Basu case study received potassium and magnesium replacement during her first 2 pregnancies, but did not receive any intervention during her third pregnancy. Her pregnancy was uncomplicated in all 3 cases. The second patient, a 33 year old reported in the Mascetti case study did not receive any intervention and experienced tiredness and tetanic seizures during pregnancy, but delivered a healthy baby at 38 weeks. Finally, a 3rd woman who did not receive any potassium or magnesium supplementation received a homeopathic intervention instead, not fully described in the Mascetti case study. Her pregnancy was uncomplicated.

**Serum K⁺ and Mg²⁺ levels**

The range for serum K⁺ levels was 2.0 – 4.8 mmol/L (n=23). The median highest serum K⁺ level attained during pregnancy was 3.3 mmol/L (n=23) and the median lowest serum K⁺ level was 2.5 mmol/L (n=22). The range for serum Mg²⁺ levels was 0.3 – 2.6 mmol/L (n=19). Median highest magnesium level attained during pregnancy was 0.75 mmol/L (n=19) and median lowest magnesium level was 0.5 mmol/L (n=19). Figures 1 and 2 illustrate the range of maximum and minimum serum potassium and magnesium levels reported for all cases and figures 3 and 4 illustrate the same for the patients with diuretic use during pregnancy. Among the 27 patients, only 8 patients used a potassium-sparing diuretic at some point during their gestational period [6,10,14,16,20-23]. The median highest serum K⁺ for these patients was 3.35 mmol/L (n=7) and the median lowest serum K⁺ level was 2.5 mmol/L (n=14) respectively in cases where only oral and/or IV potassium and/or magnesium supplementation was used. On the other hand, the median highest Mg²⁺ level was 0.9 mmol/L (n=5) and median lowest serum Mg²⁺ level was 0.47 mmol/L (n=5) in the diuretic group vs. 0.75 mmol/L (n=14) and 0.54 mmol/L (n=13) in the oral and/or IV supplementation group. No intervention was reported in 3 pregnancies [7,16] and the serum K⁺ and Mg²⁺ levels were reported in only 1 of these 3 cases where the maximum K⁺ level attained was 2.6 mmol/L while the minimum was 2.4 mmol/L. The maximum magnesium level attained was 0.58 mmol/L while the minimum was 0.53 mmol/L. In most patients, potassium and magnesium levels normalized post-partum.

**Impact on Fetus**

Fetal complications were observed in several of the pregnancies featured in the case studies. Oligohydramnios was seen in six of the cases [6,9,15,17,18] all of which received potassium and magnesium supplementation during pregnancy, with one patient also receiving spironolactone [6]. Placenta previa and intrauterine growth restriction (IUGR) accompanied the oligohydramnios in one of these cases [9]. In a different case, the oligohydramnios was noted at 28 weeks, along with severe intrauterine growth restriction (growth on 3rd percentile) and
absence of fetal cardiac activity [17]. Severe IUH with reversed end-diastolic placent al flow was seen in a separate pregnancy despite IV potassium and magnesium replacement [13]. This baby was delivered at 28 weeks of gestation with the lowest fetal weight, weighing only 636g among the live births reported in the 27 cases. This particular patient had a history of 3 prior miscarriages and a prior fetal demise.

Delivery and Maternal-Fetal Outcomes

Most of the reported deliveries were spontaneous vaginal births with ten being C-sections (Table 1 (included as supplementary)). One was a C-section due to breech presentation, another because of macrosomia, and the remaining two due to arrest of labor. Most of the babies were born healthy, with an overall median and mean weight of 2.93 kg (n=22). Gender was reported for 26 babies and 11 were male while 15 were females. No post-delivery complications were noted in the eight cases where potassium-sparing diuretics were used during pregnancies. All babies were born healthy with a median weight being 2.94 kg and mean weight being 2.99 kg (n=7) in the diuretic group. The median weight was 3.12 kg and the mean weight was 2.98 kg (n=15) in the non-diuretic group. Two cases of spontaneous fetal demise were reported despite being on oral and/or IV supplementation. The only newborn morbidity reported in the non-diuretic case was a case of NICU stay for 14 days for the baby and one case of very low birth weight, 636 g. No post-partum mortalities or morbidities were reported in the diuretic group.

DISCUSSION

Maintaining normal levels of serum potassium and magnesium levels and keeping the patients asymptomatic has been challenging in pregnant patients with Gitelman’s syndrome [7,20]. While the use of either oral or IV supplementation is considered a must for maintaining normal electrolyte levels during pregnancy, [9,13,14,16,21,22,24] no standardized guidelines have been made regarding the use of potassium-sparing diuretics for electrolyte management in pregnant patients with this condition. In our review of the 27 case studies with a total of 33 pregnancies reported in patients with Gitelman’s syndrome, we found that multiple treatment approaches have led to favorable pregnancy outcomes. IV or oral supplementation was reported in 29 pregnancies, the use of potassium-sparing diuretics was reported in 8, and no treatment or alternative treatment (homeopathy) was reported in 3 cases. Among the diuretics group, the use of spironolactone was reported in 4 cases, amiloride in 4, and the use of eplerenone was reported in 2 cases. The normal serum K⁺ level range is 3.5 – 5.0 mmol/L and the normal serum Mg²⁺ level is 1.5 – 2.0 mmol/L. In our review of the 27 cases, the median overall maximum serum K⁺ level was 3.3 mmol/L and the median minimum was 2.5 mmol/L. The median overall maximum serum Mg²⁺ level was 0.75 mmol/L and the median minimum was 0.5 mmol/L.

Even though most patients were hypokalemic and hypomagnesemic throughout pregnancy as seen in figures 1, 2, 3, and 4 despite using some form of K⁺ and Mg²⁺ replacement and/or potassium-sparing diuretics, the outcomes of pregnancies were mostly normal. 31 of the 33 pregnancies resulted in the delivery of healthy neonates without any post-partum complications. Seven of the 33 babies were born pre-term and one of those babies was reported to have had a 14-day NICU stay until lung maturation while another was born severely premature at 28 weeks, weighing only 636 g. However, all the pre-term, term, and post-term pregnancies resulted in babies without any long-term post-partum complications. The mean and median weights for all live-births was 2.93 kg (n=22). Fetal loss was reported in 2 cases despite the patients being on potassium and magnesium supplementation.

While the use of oral or IV potassium and magnesium
supplementation is considered a must for treating pregnant patients with Gitelman’s syndrome, the use of potassium-sparing diuretics is less so, owing to the potential for teratogenic side-effects found in animal studies [14,25] and the lack of studies highlighting the long-term effects of using potassium-sparing diuretics in pregnant patients. In our review we found that there was not a significant difference in serum potassium or magnesium control throughout pregnancy or fetal outcomes in terms of birth weight or post-operative complications in patients in whom the diuretics were used. The median maximum potassium level achieved during pregnancy in the diuretic group was 3.35 mmol/L while in the non-diuretic group it was 3.4 mmol/L. The median minimum level was 2.5 mmol/L in both groups. The magnesium levels, however, showed a little more variance in the two groups. The serum magnesium levels appeared to be better controlled in the diuretic group (median maximum serum Mg\(^2+\) = 0.9 mmol/L vs. 0.75 mmol/L in the non-diuretic group). However, the median minimum levels were lower in the diuretic group than in the non-diuretic group (0.47 mmol/L vs. 0.54 mmol/L). Additionally, the neonate birth weights were not significantly different in the two groups. The mean birth weight in the diuretic group was 2.99 kg while the mean birth weight in the non-diuretic group was 2.98 kg. Only 1 of the 8 neonates was born pre-maturely in the diuretic group [6] while 6 of the 24 neonates in the non-diuretic group were reported to be born prematurely. Oligohydramnios was seen in only 1 patient in the diuretic group while it was reported in 5 cases in the non-diuretic group. Additionally, complications such as a partial placenta previa, IUGR, and reversed end-diastolic placental flow were only seen in the non-diuretic group patients. Moreover, maternal complication such as GDM was seen in 1 patient in the diuretic group compared to 2 in the non-diuretic group.

The clinical condition of the patients during pregnancy varied greatly on a case-to-case basis and we divided it into three major categories: asymptomatic, mild to moderate symptoms, and severe symptoms. We included patients with nausea, intermittent emesis, mild hyperemesis, muscle cramps, fatigue, and paresthesias in the mild-to-moderate category while patients with diffuse muscle paralyses, seizures, dizziness, syncope, prolonged QT with V-tach were included in the severe category. Most of the patients fell in the mild-moderate category. Symptomatically, the diuretic group patients appeared to have done much better. All of the patients in this group were either asymptomatic or had mild hyperemesis, paresthesias or muscle cramps. None of these patients had any severe symptoms. One of these patients however, required 39 admissions for IV potassium replacement despite being on oral supplementation and spironolactone later replaced by amiloride. Additionally, no teratogenic effects of using potassium-sparing diuretics were noted in those who received these diuretics. There was no feminization of the male fetus in the patients who used spironolactone although in some cases, spironolactone was switched to amiloride owing to the relatively safer drug profile of the latter. Eplerenone was used in 2 cases and resulted in favorable fetal outcomes without any complications. No post-partum fetal morbidity or mortality was reported in the diuretics group.

Overall, our literature review shows that the most pregnancies regardless of the intervention used, resulted in favorable outcomes in pregnant patients with Gitelman’s syndrome despite persistent hypokalemia and hypomagnesemia. Although no formal studies have been done to compare the outcomes of using potassium-sparing diuretics vs. IV and oral potassium and magnesium supplementation, our review suggests that adding diuretics to the regimen results in better symptomatic control and lower rates of premature births, fetal demise, and gestational complications, without compromising the birth weights of the neonate or the levels of serum potassium and magnesium levels attained during the pregnancies. Additionally, the feared complications of feminization of the male fetus or teratogenic effects of other potassium-sparing diuretics were not seen in any of these cases.

Although, a recommendation on whether or not to use potassium-sparing diuretics for the correction of serum electrolyte levels in pregnant patients with Gitelman’s syndrome cannot be made without conducting an official randomized controlled trial, our literature review does show that the use of diuretics in pregnancy resulted in favorable maternal and fetal outcomes with better symptom control in pregnant patients with Gitelman’s syndrome.

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REFERENCES


