Exceptional Case

Gitelman syndrome and pregnancy

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Abstract
Gitelman syndrome (GS) is an autosomal-recessive condition characterized by hypokalemia, hypomagnesemia and hypocalciuria. Very little information is available in the literature to guide the management of pregnant patients with GS. We report a case of a 27-year-old woman with GS who became pregnant and despite persistent hypokalemia and hypomagnesemia during pregnancy and labor, had a successful maternal and fetal outcome.

Keywords: Gitelman syndrome; hypokalemia; pregnancy

Introduction
Gitelman syndrome (GS) is a rare autosomal-recessive inherited disorder with 99% penetrance caused by inactivating mutations in the SLC12A3 gene, localized on the 16q13 chromosome. This genetic defect impairs the function of the thiazide-sensitive sodium-chloride cotransporter in the distal convoluted renal tubule. GS is the hypocalciuric, hypomagnesemic variant of Bartter syndrome, which was first described in 1966 [1]. The impact of this condition on maternal and fetal outcome is still unclear. Here, we describe the management and pregnancy course of a 27-year-old patient with GS.

Case presentation
We report the course of a pregnancy in a 27-year-old woman previously diagnosed with GS. Her pregnancy was uneventful and she remained asymptomatic despite persistent hypokalemia. Potassium levels were followed at a regular basis and ranged between 2.3 and 3.1 mmol/L (2.3 and 3.1 mEq/L). She was electively admitted to hospital at 39 weeks of gestational age for full-term induction of labor. A PICC line was placed to allow replacement of electrolytes. The patient received 240 mEq of intravenous potassium chloride and 180 mEq per oral, as well as 4 g of intravenous magnesium sulfate and 1200 mEq of oral magnesium oxide. She was continued on 150 mg daily of eplerenone. Despite aggressive electrolyte replacement, her potassium and magnesium levels ranged between 2.0 and 3.0 mmol/L (2.0 and 3.0 mEq/L) and 1.1 and 2.6 mmol/L (1.1 and 2.6 mEq/L), respectively. The baby was born healthy with 2863 g, and Apgar measurements were 8 and 9 at 1 and 5 min, respectively. She was discharged two days after giving birth and has remained symptom free.

Discussion
First described in 1966 by Gitelman et al., GS is a rare autosomal-recessive condition characterized by hypokalemia, metabolic alkalosis and hypomagnesemia [1]. It has since been shown to result from a mutation in the SLC12A3 gene on chromosome 16 leading to a loss of function mutation in the sodium-chloride cotransporter in the distal convoluted tubule. This leads to potassium and magnesium wasting into the cortical collecting duct as the increase in delivered sodium is reabsorbed through the epithelial sodium channel. Despite being normotensive, the patients clinically have activation of the renin–angiotensin–aldosterone axis [2]. To date, 24 pregnancies in 18 women with GS have been described in the literature [3–15]. Twenty of the pregnancies had no reported fetal complication (Table 1), six pregnancies were complicated by oligohydramnios [5, 8, 9, 12, 13] and one was complicated by intrauterine growth retardation [8]. The management of maternal GS during pregnancy continues to be a challenge. Renin, angiotensin II and aldosterone levels are known to increase during pregnancy [16]. Kaliuresis does not typically ensue presumably due to the antimineralocorticoid effects of progesterone demonstrated by Ehrlich and Lindheimer in 1972 [17]. De Haan et al. have suggested that this protective mechanism may be impaired in GS patients thus resulting in an exacerbation of potassium and magnesium losses [8]. Oral potassium and magnesium supplements continue to be the mainstay of therapy. The increase in the requirement for oral potassium during pregnancy has been documented by several authors including Talaulikar et al. in 2005 who reported a 6-fold increase in potassium and magnesium requirements in their patient [7]. Six of the pregnancies document the use of intravenous potassium [7–12]. Intravenous magnesium was required in three cases [7–9]. Two authors report achievement of
Table 1. Summary with the cases of Gitelman syndrome during pregnancy

| Author                | Age at diagnosis (years) | Diagnosis                                                                 | Maternal age (years) | Number of patients | Number of pregnancies | Symptoms                                                                                                                                                                                                 |
|-----------------------|--------------------------|---------------------------------------------------------------------------|----------------------|--------------------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jones JM et al. [5]   | 35                       | 1st trimester                                                             | 35                   | 1                  | 2                     | Initially presented with new onset of seizures. N/A 1st - asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Basu A et al. [6]     | 17                       | Before pregnancy                                                          | 37                   | 1                  | 3                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Talaulikar GS et al. [7] | 20                     | Before pregnancy                                                          | 37                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Kwan et al. [10]      | 20                       | Before pregnancy                                                          | 24                   | 1                  | 3                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Srinivas SK et al. [11] | 17                      | 2nd trimester (17 weeks)                                                  | 37                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| De Hoan J et al. [8]  | N/A                      | Before pregnancy                                                          | 24                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| De Arriba G et al. [12] | 18                    | Before pregnancy                                                          | 24                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Daskalakis G et al. [13] | 20                     | 1st trimester (10 weeks)                                                  | 24                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| McCarthy FP et al. [9] | 32                      | 1st trimester (9 weeks)                                                   | 32                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Raffi et al. [14]     | 22                       | Before pregnancy                                                          | 27                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Morton A et al. [15]  | 21                       | Before pregnancy                                                          | 27                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Mascetti L et al. [4] | N/A                      | Before pregnancy                                                          | 24                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |
| Calo LA et al. [3]    | N/A                      | Before pregnancy                                                          | 24                   | 1                  | 2                     | N/A 1st- asymptomatic except for tiredness in 3rd trimester 2nd- asymptomatic 3rd- asymptomatic 1) Increasing tiredness, muscle cramps. Required 3 hospitalizations 2) Not described Nausea, vomiting, proximal lower extremity muscle weakness, VF arrest, seizures, prolonged QTc |

Gestational complications

| Oligohydramnios       | Delivery                  | Neonate                      | Gestational age | Potassium values | Magnesium values | Treatment                                                                                                                                                                                                 |
|-----------------------|---------------------------|------------------------------|-----------------|------------------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Induced vaginal delivery  | Induced vaginal delivery | Healthy male infant, 2509 g | 37 weeks        | ~3.2 mEq/L       | ~1.3 mEq/L       | K and Mg supplementation                                                                                                                                                                                |
| Oligohydramnios       |                           | Healthy female infant, 2410 g| 36 weeks        | N/A              | N/A              | K and Mg supplementation                                                                                                                                                                                |
| 1, 2 and 3) None      | 1st- spontaneous labor   | Healthy infant, 2620 g       | 1st-35 weeks    | 1st- K range = 2.3-2.8 mmol/L | 1st- Mg range = 0.53-0.58 mmol/L | 1st- K and Mg supplementation 2nd-K and Mg supplementation 3rd- K and Mg supplementation 1 and 2) K and Mg supplementation |
| 2nd- spontaneous labor| Healthy female infant, 2910 g | 2nd-38 weeks                | N/A             | N/A              | N/A              | 1 and 2) K and Mg supplementation                                                                                                                                                                        |
| 3rd- spontaneous labor| Healthy female infant, 3480 g | 3rd-38 weeks                | N/A             | N/A              | N/A              | 1 and 2) K and Mg supplementation                                                                                                                                                                        |
| 1) None               | Normal delivery           | Healthy infant               | 1) N/A          | K range = 2.3-3.4 mmol/L | 1 and 2)N/A      | 1 and 2) K and Mg supplementation                                                                                                                                                                        |
| 2) Gestational diabetes| Elective C-section       | Healthy female infant, 3250 g| 2) 39 weeks     | N/A              | N/A              | K and Mg supplementation                                                                                                                                                                                |
| None                  |                           | N/A                          | 41 weeks and 4 days | N/A              | N/A              | K and Mg supplementation                                                                                                                                                                                |
| Oligohydramnios       | Programmed C-section     | Healthy infant, 3970 g       | 1 and 2) 38 weeks | N/A              | N/A              | K and Mg supplementation. 1st case required i.v. supplementation                                                                                                                                          |
| Oligohydramnios       | w/o complications        | Healthy male infant, 3845 g  | N/A             | N/A              | N/A              | K and Mg supplementation. K and Mg supplementation. 1st case required i.v. supplementation                                                                                                                                                                                |
| Oligohydramnios       | Elective C-section (breech presentation) | Healthy female baby, 3350 g | N/A             | Maximum level = 3.0 mmol/L | Maximum level = 0.68 mmol/L | K and Mg supplementation. K and Mg supplementation. 1st case required i.v. supplementation                                                                                                                                 |

(continued)
potassium levels in the 3.6–4 mmol/L (3.6–4.0 mEq/L) range [10, 14]. The remainder of the documented cases had peak potassium levels ranging from 2.8 to 3.3 mmol/L (2.8–3.3 mEq/L). It has been suggested that normalization of potassium and magnesium levels is not required for a good obstetric and neonatal outcome [6]. Worsening of the symptoms of GS such as fatigue, cramping, tetany and dizziness has been described in the GS pregnancies [7, 12, 13]. The symptoms may be exacerbated by hyperemesis and fetal demand for potassium [9, 12]. Worsening of symptoms is cited as a reason for the modification of therapy [3, 4, 6–11, 13]. Our patient did not exhibit symptoms during her pregnancy, and we felt that intravenous potassium loading would be inefficient and unnecessary in the absence of symptoms. Beyond the use of supplemental cations, the management of patients with GS has included the use of potassium-sparing diuretics. The US Food and Drug Administration has deemed spironolactone a category C drug in pregnancy. De Arriba et al. describe the use of spironolactone in one pregnancy [12]. The authors note that no feminization was seen in the male newborn. This is consistent with the findings of Mascetti et al. who describe a series of spironolactone-exposed children born to a group of mothers with Bartter syndrome, another potassium-wasting nephropathy [4]. The use of amiloride and eplerenone, both class B drugs in pregnancy, has been previously documented in GS [4, 9, 14, 15]. In contrast to Bartter syndrome, the use of non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit prostaglandin synthase is theoretically of no benefit as GS is not a hyperprostaglandinemic state [18]. There is a risk of a lack of ductus arteriosus closure with NSAID use. Angiotensin-converting enzyme inhibitors are contraindicated in pregnancy due to teratogenic effects as well as impaired fetal growth. There has been a concern over the potential for a ventricular tachyarrhythmia during pregnancy and childbirth due to hypokalemia. Fortunately, no such complication has been observed in any of the documented GS pregnancies. The extensive work of Calo et al. in this area suggests however that the upregulation of the nitric oxide system and vasodilation seen in GS may limit the physiologic response to increased myocardial demand [19, 20]. It is also suggested in subsequent work that increased angiotensin 1–7 levels seen in GS may be antiarrhythmic at low levels and proarrhythmic at very high levels [21]. The small number of documented GS pregnancies precludes any rigorously studied recommendations for management in the peripartum period. The anesthesia literature describes a risk of complications in GS patients in the peripartum setting. These include electrocardiographic changes as well as vasodilation, electrolyte imbalance and alkalemia complicating the ventilatory management of the patient [22]. Uneventful spinal anesthesia for cesarean delivery is also described in the literature [23]. Given the expected physiologic demands of labor and delivery, it appears that an elective, multidisciplinary approach to the delivery of the child is most prudent. Baseline electrocardiography should be obtained as up to 50% of patients with GS

| Gestational complications | Delivery | Neonate | Gestational age | Potassium values | Magnesium values | Treatment |
|---------------------------|----------|---------|----------------|-----------------|-----------------|-----------|
| Oligohydramnios           | Induced C-section (failure to progress in the first stage) | Healthy female baby, 2940 g | 266 | K range = 2.6–3.3 mmol/L | Mg range = 0.47–0.66 mmol/L | K and Mg supplementation, amiloride. Required 39 hospitalizations i.v. supplementation of K and Mg | K and Mg supplementation, amiloride (1st trimester). Required 1 hospitalization for i.v. supplementation of K and Mg. Epleronone |
| Fetal macrosomia (patient had gestational diabetes) | Induced C-section | Healthy male baby, 5080 g | N/A | N/A | N/A | K and Mg Homeopathy K, amiloride K, Mg None (1st pregnancy) / K (2nd pregnancy) |
| None                      | Vaginal delivery | Healthy female baby, 3630 g | 273 | 2.6–2.9 mmol/L | N/A | K and Mg supplementation, amiloride (1st trimester). Required 39 hospitalizations i.v. supplementation of K and Mg. Epleronone |
| 1, 2, 3, 4 and 5) None     | N/A | Healthy male baby, 4080 g | 40 weeks | N/A | N/A | K and Mg Homeopathy K, amiloride K, Mg None (1st pregnancy) / K (2nd pregnancy) |
| 1 and 2) None              | N/A | Healthy female baby, 3380 g | 37 weeks | N/A | N/A | K and Mg Homeopathy K, amiloride K, Mg None (1st pregnancy) / K (2nd pregnancy) |
|                           | N/A | Healthy male baby, 2900 g | 38 weeks/36 weeks | N/A | N/A | K and Mg Homeopathy K, amiloride K, Mg None (1st pregnancy) / K (2nd pregnancy) |
|                           | N/A | Healthy female baby, 3125 g | At term/At term | N/A | N/A | K and Mg Homeopathy K, amiloride K, Mg None (1st pregnancy) / K (2nd pregnancy) |
have QT interval prolongation. Cardiac telemetry and central venous access should be considered at the time of delivery. Frequent monitoring of electrolytes is advisable as is blood pressure monitoring given the propensity of GS patients have vasodilation. A drop in serum potassium during labor is not previously described in the literature. The postpartum period is associated with natriuresis; however, this would not explain a drop in potassium during active labor. It may be, however, that the drop in serum potassium observed here is related to a shift in potassium from the extracellular to intracellular space as could be seen in any patient and is not unique to GS. In our patient, we suspect that increased β-adrenergic tone may have played a role. The effects of epinephrine on hypokalemia were described in 1983 by Struthers et al. Pretreatment with a thiazide diuretic was associated with a more significant drop in serum potassium during epinephrine loading than that seen in the control group receiving epinephrine alone [24]. As GS mimics the effects of thiazide diuretics, one could assume a similar effect in these patients. Cellular shift of potassium may also occur because of rising blood glucose concentrations.

In conclusion, the experience of clinicians treating pregnant women with GS is limited but is also being described with more frequency. There is no evidence of significant risk to the fetus but maternal symptoms may worsen during the pregnancy. The management of GS should be focused on the replacement of potassium and magnesium though routine intravenous supplementation and should be reserved for cases of worsened symptoms. Cautious use of adjunctive treatment with potassium-sparing agents should be considered as the potassium requirement may increase significantly during pregnancy. In addition to GS-related potassium and magnesium loss, hypokalemia can be exacerbated by cellular shift as well as extrarenal losses of cations which can affect any patient. No consensus recommendations exist for the perinatal management of the pregnant GS patient but an elective delivery in a setting with appropriate cardiac monitoring and central venous access is prudent as potassium and magnesium aberrations during active labor may be seen.

Conflict of interest statement. None declared.

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