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Pregnancy in glycogen storage disease type Ib: gestational care and report of first successful deliveries

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Abstract

Patients with type Ia glycogen storage disease (GSD) have been surviving well into adulthood since continuous glucose therapy was introduced in the 1970s, and there have been many documented successful pregnancies in women with this condition. Historically, few individuals with type Ib GSD, however, survived into adulthood prior to the introduction of granulocyte colony stimulating factor (G-CSF) in the late 1980s. There are no previously published reports of pregnancies in GSD type Ib. In this case report we describe the course and management of five successful pregnancies in three patients with GSD type Ib. Patient 1 experienced an increase in glucose requirement in all three of her pregnancies, starting from the second trimester onwards. There were no major complications related to neutropenia except for oral ulcers. The infants did well, except for respiratory distress in two of them at birth. Patient 2 used cornstarch to maintain

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euglycemia, but precise dosing was not part of her regimen, and, hence, an increase in metabolic demands was difficult to demonstrate. She developed a renal calculus and urinary tract infection during her pregnancy and had chronic iron deficiency anemia but no neutropenia. The neonate did well after delivery. Patient 3 had poor follow-up during pregnancy. Increasing glucose requirements, worsening lipid profile, neutropenia associated with multiple infections, and anemia were noted. The newborn infant did well after delivery. In addition to the case reports, the challenges of the usage of G-CSF, the treatment of enterocolitis, and comparisons with the management of GSD Ia are discussed.

Introduction

The glucose 6-phosphatase (G6Pase, E.C. 3.1.3.9) enzyme catalyzes the final reaction of both glycogenolysis and gluconeogenesis. This critical reaction results in hydrolysis of glucose 6-phosphate (G6P) to yield glucose and phosphate. The G6P transporter transfers G6P into the endoplasmic reticulum for hydrolysis by G6Pase. Glycogen storage disease (GSD) type Ia is caused by deficiency of G6Pase, while GSD type Ib is caused by deficiency of the G6P transporter. Both disorders result in impaired endogenous glucose production, and the shunting of G6P into various pathways during glycogenolysis leads to hyperuricemia, hypertriglyceridemia and hyperlactatemia (Wolfsdorf and Weinstein 2003).

Patients with type Ia GSD have been surviving well in to adulthood since continuous glucose therapy was introduced in the 1970s, and there have been many documented successful pregnancies in women with this condition (Farber et al. 1976; Johnson et al. 1990; Martens et al. 2008; Ryan et al. 1994). The main concerns associated with pregnancy in patients with GSD Ia include increased carbohydrate requirement in the first trimester and near term, metabolic derangement, decreased glomerular filtration rate, especially in the setting of renal insufficiency prior to pregnancy, and the possibility of adenoma rupture (Martens et al. 2008). As GSD type Ib, however, is also associated with neutropenia and Crohn-like inflammatory bowel disease, historically, few individuals survived into adulthood prior to the introduction of granulocyte colony-stimulating factor (G-CSF) in 1989 (Visser et al. 2000). This is the first generation of patients with GSD Ib to survive to adulthood, and there are no previously published reports of pregnancies in women with this condition. In this case report, we describe the course and management of five successful pregnancies in three patients with GSD type Ib. The challenges of treatment of neutropenia and enterocolitis are discussed, in addition to comparisons of the management of GSD Ia.

Case reports

The case reports are summarized in Tables 1 and 2.

Case 1

Patient 1 was diagnosed with GSD Ib at 2 months of age during an evaluation for lethargy. The diagnosis was confirmed by liver biopsy, and type Ib GSD was subsequently confirmed by mutation analysis, which revealed that she was a compound heterozygote for the S55R/Q218X mutations. She had been hospitalized for hypoglycemia once in childhood. Her medical history was otherwise remarkable for intermittent neutropenia not requiring G-CSF. Patient 1 had never developed inflammatory bowel disease, and she was not on any medications prior to her pregnancies. She was not on cornstarch, and she maintained euglycemia by intermittent glucose administration.

During her first pregnancy, her glucose concentrations were maintained with hourly doses of dextrose solutions taken orally throughout the day and via nasogastric tube at night. She

monitored her own glucose and lactic acid levels frequently, using portable home monitors, and the dosage of dextrose was increased appropriately throughout the pregnancy to maintain glucose concentrations above 75 mg/dl (4.2 mmol/l) and lactic acid levels below 2.0 mmol/l. Her glucose requirement increased consistently throughout pregnancy, from the second trimester onwards. Her kidney function and liver ultrasounds remained normal throughout the pregnancies. Despite having neutropenia, she did not develop any infections, but chronic oropharyngeal ulcers were problematic.

The first baby was delivered at 39 weeks gestational age via a spontaneous vaginal delivery with a prolonged latent stage of labor. Active pushing progressed for 2.5 h. Two doses of meperidine hydrochloride were given in early labor, followed by increased doses of oxytocin. Her blood glucose was maintained above 108 mg/dl (6 mmol/l) throughout delivery with intravenously administered 10% dextrose (D10 half-normal saline solution) run at 110 ml/h. Lactic acid was also monitored during delivery and remained below 2 mmol/l. Continuous epidural analgesia was provided. A 3,325 g baby girl was born with Apgar scores of 6 after 1 min and 7 after 5 min. She was hypotonic following delivery, and she was admitted to the neonatal intensive care unit, where she required continuous positive airway pressure (CPAP) support for 24 h. She remained in the hospital for 1 week to establish feeding and for treatment of neonatal jaundice with phototherapy. The post-partum course was uneventful, and the mother was weaned off the intravenously administered dextrose within 4 h. Several weeks following discharge, patient 1 was readmitted with epiglottitis in the setting of neutropenia, and transient G-CSF therapy was required.

During the second pregnancy, patient 1 experienced frequent nausea that was not associated with vomiting. Once again, her blood glucose and lactic acid levels were monitored closely throughout the pregnancy, and the patient self-titrated her glucose to maintain normal glucose and lactate concentrations. During the course of the pregnancy, her glucose requirement steadily increased, from the second trimester onwards. At baseline, she required 14.4 g of glucose per hour to maintain normoglycemia at rest. Her glucose requirement rose to 19.8 g per hour at night during the second trimester and peaked in the third trimester, at 20.5 g per hour. An uncomplicated spontaneous vaginal delivery occurred at 39 weeks gestational age. The patient was again given an intravenous infusion of D10 half-normal saline solution during labor. She had continuous epidural analgesia and an oxytocin infusion. The labor involved 30 min of active pushing before the delivery. Her 3,238 g son earned Apgar scores of 9 and 9 at 1 min and 5 min, respectively.

In the third pregnancy, as with her prior pregnancies, the patient monitored her glucose and lactate levels and self-adjusted with the advice of the medical team to maintain normal concentrations. Her glucose requirement increased from 14.4 g/h to 21.6 g/h through the pregnancy, starting in the second trimester. She had significant discomfort related to varicose veins in the lower extremities, starting at 13 weeks of gestation. A color Doppler ultrasound of the lower extremities after 5 months of gestation was remarkable for superficial varicosities. At 34 weeks of gestation, the patient noticed a tender mass in her right groin, accompanied by a significant increase in size of her right thigh compared to her left. A diagnosis of venous thrombosis was made, and low molecular weight heparin therapy was initiated. Labor was induced at 35 weeks of gestation, and a baby girl was born weighing 2,528 g. The baby was admitted to the neonatal intensive care unit for CPAP support. She remained in the hospital for 2 weeks and required feeding by nasogastric tube. The venous thrombosis in patient 1 resolved shortly after delivery.

Abdominal ultrasound performed after each pregnancy demonstrated hepatomegaly with no focal lesions or adenomas. The patient had neutropenia during all of her pregnancies. Occasional oral ulcers were the only manifestation, and the patient was not given G-CSF

during the pregnancies. Her hepatic transaminases, triglycerides, and uric acid concentrations remained normal through all three pregnancies.

Case 2

Patient 2 was of Afro-Caribbean heritage. Records of her clinical course throughout childhood were not available. It is believed that she had been diagnosed with type I glycogen storage disease by liver biopsy. Type Ib GSD was suggested as a result of her history of intermittent neutropenia and recurrent infections. Mutation analysis confirmed the presence of the R415X mutation on one allele. The second mutation was not identified.

Patient 2 had outstanding metabolic control, and, at 30 years of age, she became pregnant. Cornstarch therapy was used as the primary treatment modality, but precise dosing of cornstarch was not part of her treatment regimen. At 19 weeks of gestation, she had moderate microscopic hematuria noted on a screening urinalysis, and she was empirically treated for a urinary tract infection. Subsequent testing performed as a result of persistence of the hematuria revealed the presence of albuminuria, which remained stable throughout the pregnancy. Her hematuria continued to worsen, progressing to frank hematuria in the third trimester. Anemia and iron deficiency also worsened throughout pregnancy. Hemoglobin was 9.2 g/dl, 7.3 g/dl, 6.9 g/dl and 6.9 g/dl at 10 weeks, 19 weeks, 30 weeks and 35 weeks, respectively. Her mean corpuscular volume and mean corpuscular hemoglobin concentration were, respectively, 67.8 fl and 20.5 pg at 30 weeks and 64.4 fl and 19 pg at 35 weeks. At 30 weeks of gestation, a comprehensive evaluation for anemia was performed, including normal hemoglobin electrophoresis, and only iron deficiency was identified. Neither neutropenia nor additional infections developed.

At 36 weeks and 5 days, she had an elective C-section performed due to uterine fibroids. Intravenous administration of glucose was commenced prior to her surgery, and she did well, with no documented hypoglycemia. Her 2,940 g son emerged vigorously, with a pH of 7.4, and he earned Apgar scores of 9 and 9 after 1 min and 5 min, respectively. There were no difficulties with the post-natal transition. Following the delivery, the patient remained with persistent hematuria, and an intravenous pyelogram performed 6 weeks after delivery confirmed the presence of a left renal calculus.

Case 3

Patient 3 had been diagnosed as having type I GSD by liver biopsy at 13 months of age. Her presenting signs and symptoms were hepatomegaly, irritability, difficulty sleeping, and hypoglycemia. Molecular testing showed that she was homozygous for the G339C mutation. During infancy, the patient developed frequent infections at her gastrostomy site. She was maintained on overnight pump feeds until 11 years of age, at which time she was started on frequent intermittent cornstarch feeds administered throughout the day and night. At the same visit, G-CSF was started for a short period as part of a study. Beyond the study period, the patient was not given G-CSF, and her absolute neutrophil count ranged from 1,495/ μ l at 15 years of age to 570/ μ l at 17 years of age. Normal microalbumin:creatinine ratios were noted until she reached 14 years of age. Just prior to becoming pregnant, the patient was found with albuminuria with a microalbumin:creatinine ratio of 149 mg/g. Hypertension was not present, and she was not placed on an angiotensin-converting enzyme (ACE) inhibitor for GSD nephropathy.

At 17 years and 5 months of age, the patient was found to be 6 weeks pregnant. Her absolute neutrophil count during pregnancy was found to be 947 at 6 weeks, 626 at 17 weeks and 3,974 at 33.5 weeks of gestation. During her pregnancy, she had two episodes of tonsillopharyngitis, and one episode of oral ulceration following a dental procedure. She needed

antibiotics for all of the infections, but G-CSF was not used. In addition, she developed a urinary tract infection at the time of delivery. Her hemoglobin level before pregnancy was 12.6 g/dl, and it dropped to 10.7 g/dl at 33.5 weeks. At 29 weeks of gestation, hematuria was noted. The patient was diagnosed by renal ultrasound as having a kidney stone and was started on nitrofurantoin, which led to the subsequent resolution of the hematuria. Levels of liver enzymes and uric acid remained stable, but inconsistent follow-up did not allow the assessment of her renal function. At 33.5 weeks of gestation, she required an increase in her cornstarch dose from 35 g per dose twice at night to 42 g per dose twice at night, due to hypoglycemia (50–60 mg/dl) in the early morning hours and a rise in triglyceride levels to 420 mg/dl from 153 mg/dl. She maintained her blood glucose level during the day by frequent feeding. No cornstarch was used during the day. The patient delivered her baby after 39 weeks and 2 days of gestation. Her labor was induced, and she endured 7–10 h of labor. Epidural analgesia was administered through this duration. A boy was born weighing 4,260 g. He had mild physiological jaundice that did not require treatment. One low blood sugar reading of 50 mg/dl was noted within 24 h of the birth. The baby was fed and the blood sugar level normalized. The newborn infant did well, and there were no complications. The mother had had no liver adenomas prior to pregnancy, and a repeat ultrasound after her pregnancy was normal.

Discussion

Patients with glycogen storage disease are now surviving into adulthood, and pregnancies are now becoming common. While successful pregnancies have been documented in women with GSD types 0, Ia, III, and IX (Bhatti and Parry 2006; Confino et al. 1984; Farber et al. 1976; Johnson et al. 1990; Lee 1999; Martens et al. 2008; Ryan et al. 1994), successful pregnancies in women with type Ib GSD have not been previously described. The rarity of the disease (1 in 1 million live births) and the limited previous survival of adults likely are the principle reasons related to the lack of prior births. With the introduction of G-CSF in 1989, the prognosis for those with GSD Ib improved dramatically, and the frequency of pregnancies in women with this condition is expected to increase (Abe et al. 2000).

As with all types of GSD, close monitoring of biochemical control is required during pregnancy. Vomiting during the first trimester, associated with morning sickness, can be problematic, and intravenous glucose support may be required when cornstarch or feeds cannot be tolerated. Glucose requirement increases steadily in the third trimester in all types of hepatic glycogenoses, and this was again seen in all our pregnant patients (Martens et al. 2008). There appeared to be a large difference in the increase in glucose requirement between patients 1 and 3. Patient 3 probably had a higher glucose requirement than what was consumed, as evidenced by a marked increase in triglyceride levels, demonstrating poor metabolic control. Glucose monitoring should be used in the titrations during therapy to keep the glucose concentrations above 75 mg/dl (4.2 mmol/l). Lactic acidosis can be problematic in some patients with GSD Ib, and monitoring is advisable if there are persistent elevations above 2 mmol/l, due to the possibility of premature labor.

Other challenges in common with GSD Ia include metabolic derangement related to poor control, such as hypertriglyceridemia and hyperuricemia. These abnormalities are the result of increased glycogenolysis, and they were particularly apparent in patient 3, when control was suboptimal. While the high estrogen state associated with pregnancy has been reported to result possibly in increased adenoma formation and adenoma growth, this complication was not seen in our cohort (Terkivatan et al. 2000). As seen in the population with type Ia, worsening of renal function during pregnancy was noted. Increased albuminuria was detected in two of our three patients during pregnancy, and close monitoring of renal status in future pregnancies will be critical, since chronic worsening of renal function has been

seen previously in other forms of GSD (Abe et al. 2000; Calhoun et al. 1996; Dale et al. 2003; Fujiwaki et al. 1995; Fung et al. 2005; Kaufmann et al. 1998; Martens et al. 2008; Sangalli et al. 2001). It is noteworthy that two of our three patients had renal calcification develop during pregnancy. This complication has not been commonly seen in GSD type Ia pregnancies, yet the risk of stone formation is typically much higher at baseline in GSD type Ia than in type Ib (Weinstein et al. 2001).

While there are many similarities between GSD Ia and Ib, there are some challenges unique to the population with GSD type Ib. Neutropenia is almost universal in patients with this disease, and low neutrophil counts were documented during four of the five pregnancies. While severe infections did not occur in this cohort during their pregnancies, infectious complications occurred either during pregnancy or in the perinatal period in all three mothers. It is notable that the condition in this cohort may be milder than in many of the patients with GSD Ib, as none had overt signs of inflammatory bowel disease and none of the mothers was on G-CSF at baseline. Unlike this cohort, most patients with GSD Ib have persistent neutropenia and require long-term G-CSF therapy to prevent life-threatening infections. G-CSF is classified by the Food and Drug Administration (FDA) as pregnancy class C and is recommended to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Formal recommendations regarding G-CSF use during pregnancy are lacking, but patients with neutropenia from other causes have a higher rate of spontaneous abortions and fetal deaths. Several reports published in the literature have noted normal pregnancy outcomes after G-CSF administration during pregnancy (Abe et al. 2000; Calhoun et al. 1996; Dale et al. 2003; Fujiwaki et al. 1995; Fung et al. 2005; Kaufmann et al. 1998; Sangalli et al. 2001). Only one case report has been published that described abnormalities in a neonate following G-CSF treatment during pregnancy. The mother, however, was given the G-CSF as part of consolidation chemotherapy for acute myeloid leukemia, and it was unclear if the cardiac abnormalities and dysmorphic features present in the baby were related to any of the chemotherapeutic agents or G-CSF administration (Niedermeier et al. 2005).

GSD enterocolitis is a Crohn-like inflammatory bowel disease that has occurred in over 77% of patients with GSD Ib by adulthood (Visser et al. 2000). It is noteworthy that none of the patients in our cohort had this common complication; however, this will invariably be a co-morbidity in future pregnancies in this population. There are limited data on safety and efficacy of medical management of Crohn's disease in pregnancy (Beaulieu et al. 2009). When a child is conceived in the non-GSD patients with Crohn's disease during a period when the disease is not active, there is over a 60% chance that the disease will remain inactive during pregnancy. As medications are used during pregnancy only when there is active disease, it is difficult to differentiate the effects of the medication from the effects of active Crohn's disease itself (Mottet et al. 2007). The complications related to pregnancy outcomes associated with Crohn's disease include low birth weight, premature birth and spontaneous abortions (Baird et al. 1990; Bortoli et al. 2007; Cornish et al. 2007; Nielsen et al. 1984; Norgard et al. 2007; Woolfson et al. 1990). Bortoli et al. (2007) reported an increased incidence of congenital malformations, but it was unclear if these were related to the disease or the treatment. The mainstay of therapy in this group consists of G-CSF therapy together with 5-aminosalicylate (5-ASA) drugs such as mesalamine (Davis et al. 2008). The family of 5-ASA drugs is categorized as pregnancy category B. They seem to be safe during pregnancy (Mottet et al. 2007), and discontinuation is presently not recommended. Increased risk of low birth weight, preterm labor, and stillbirths have been reported in patients with inflammatory bowel disease (IBD) on 5-ASA drugs, but it is difficult to distinguish if these outcomes are the result of 5-ASA drug exposure or the disease activity (Diav-Citrin et al. 1998; Norgard et al. 2003). One case of renal

insufficiency in a newborn infant as a result of mesalamine use in a mother has been reported (Colombel et al. 1994).

The management of Crohn-like IBD is especially challenging in patients with GSD Ib, due to the limitation in medications that can be used. Corticosteroids cannot be used, as they increase glycogenolysis and can exacerbate lactic acidosis and hyperlipidemia in these patients. Other immunomodulators such as methotrexate, 6-mercaptopurine and azathioprine cannot be used, due to the neutropenia associated with this disease. Tumor necrosis factor- (TNF-) antagonists have revolutionized the management of inflammatory bowel disease, but their safety in pregnant women has not been well studied. Infliximab, a TNF- antagonist, is used with much success in treating non-GSD related Crohn's disease. Its use in GSD Ib is limited, as antibodies to infliximab commonly develop, and corticosteroids or other immunomodulators must be simultaneously used. These are not advisable in GSD patients, for reasons described (Davis et al. 2008). Adalimumab, also a TNF- antagonist, may be more beneficial, as it is less immunogenic, and it has been used successfully in type Ib GSD (Davis et al. 2008; Hanauer et al. 2006). Adalimumab is classified as pregnancy category B, as insufficient well-controlled studies have been conducted in pregnant women regarding the safety of this medication. Several reports (Coburn et al. 2006; Hyrich et al. 2006; Kraemer et al. 2008; Mishkin et al. 2006; O'Donnell and O'Morain 2008; Roux et al. 2007; Vesga et al. 2005) have described successful pregnancy outcomes in patients treated with adalimumab in pregnancy, and it is considered to be generally safe to use in pregnancy. A recent report based on a review of the United States Food and Drug Administration database found an increased incidence of VACTERL anomalies in children born to mothers taking the TNF- blockers infliximab and etanercept. No reports of anomalies were from women taking adalimumab (Carter et al. 2009). However, there has been an increased incidence of serious bacterial infections in patients receiving adalimumab.

With improved therapies, including extended-release cornstarch preparations and extended-release G-CSF, the prognosis for adults with GSD type Ib is continuing to improve. It is encouraging that these first pregnancies in this population have been well tolerated, but pregnancies associated with more severe neutropenia and GSD enterocolitis will invariably be more complicated. A multicenter collaborative effort is needed to best define treatment for future pregnancies, as was recently done for GSD type Ia (Martens et al. 2008).

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Abbreviations

GSD	glycogen storage disease
G6Pase	glucose 6-phosphatase
G6P	glucose 6-phosphate
G-CSF	granulocyte colony stimulating factor
CPAP	continuous positive airway pressure
D10	10% dextrose

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Table 1

Summary of mutations and complications in pregnant patients with GSD type Ib (UTI, urinary tract infection)

Patient	Mutations	Infections	Other complications
Patient 1; baby A	S55R/Q218X	Oral ulcers	None
Patient 1; baby B	S55R/Q218X	Oral ulcers	None
Patient 1; baby C	S55R/Q218X	Oral ulcers	Venous thrombosis
Patient 2	R415X/Unknown	UTI	Renal calculus, albuminuria, anemia
Patient 3	G339C/G339C	Tonsillo-pharyngitis, oral ulcers, UTI	Albuminuria, anemia, renal calculus, elevated triglyceride levels

Table 2

Summary of birth parameters and complications in newborn infants of mothers with GSD Ib

Patient	Gestational age	Birth weight (kg)	Apgar scores	Complications
Patient 1; baby A	39 weeks	3,325	6, 7	Respiratory distress, hypotonia
Patient 1; baby B	39 weeks	3,238	9, 9	None
Patient 1; baby C	35 weeks	2,528	9, 9	Respiratory distress
Patient 2; baby A	36 weeks 5 days	2,950	9, 9	None
Patient 3; baby A	39 weeks 2 days	4,260	9, 9	Transient hypoglycemia