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Short Communication

Successful pregnancy in a woman with glycogen storage disease type 6

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ABSTRACT

Glycogen storage disease type VI is caused by biallelic variants in the *PYGL* gene that result in hepatic glycogen phosphorylase deficiency. The disorder is clinically characterized by hepatomegaly and recurrent ketotic hypoglycemia from infancy. Although most patients reach adulthood without major complications, no pregnancies in women with GSD VI have been reported so far. We report on a successful pregnancy in a GSD VI patient that resulted in a healthy offspring and describe the pre- and perinatal management.

1. Introduction

Glycogen storage disease type VI (GSD VI, OMIM #232700) is a rare inherited disorder of glycogen metabolism caused by mutations in the *PYGL* gene resulting in deficiency of hepatic glycogen phosphorylase (PYGL) [1–4]. The incidence is approximately 1:65,000–1:85,000 [1]. Patients with GSD VI usually present in childhood with hepatomegaly and recurrent hypoglycemia. Other clinical symptoms comprise impaired growth resulting in short stature, osteopenia, delayed puberty and hepatic fibrosis [1,2]. Typical laboratory findings include hypoglycemia with hyperketonemia, elevated transaminase concentrations, hyperlipidemia, and reduced prealbumin concentration [1]. Most adults with GSD VI are asymptomatic [2]. As GSD VI is typically a rather mild disease, women with GSD VI usually reach the child-bearing age without major complications. Nevertheless, to our knowledge, no pregnancies in patients with GSD VI have been reported so far.

2. Case presentation

The patient is the first child of non-consanguineous parents. Clinical signs of hypoglycemia including sweating and shakiness were reported from early infancy throughout childhood. During early childhood the patient required feeding every 2 h, also at night. Hepatomegaly and elevated transaminases were first noted at 3 years. At the age of 6, a liver biopsy was performed and the diagnosis of GSD VI was made based on reduced activity of hepatic PYGL. Until age 13, the patient received regular cornstarch doses during the night, and no episodes of severe hypoglycemia were reported in the further course. From puberty until the age of 36, the patient was lost to follow-up. When she first presented to our metabolic centre at the age of 36, mild hepatomegaly was present, but otherwise she was in good metabolic control. She was on a self-chosen low-carb diet to reduce weight (body weight 113 kg, BMI 39.1 kg/m^2). Mutation analysis of the PYGL gene was performed and yielded compound heterozygosity for the variants c.475G > C (p.Gly159Arg) and c.697G > A (p.Gly233Ser). The diet was switched to a protein-rich diet with reduction of simple sugars (protein 30% of total energy). At age 38, the patient became pregnant after fertility treatment. Apart from ovarian hyperstimulation syndrome, the pregnancy was uncomplicated. Her maximum fasting time during the night was 11 h with blood glucose levels above 4.2 mmol/L in the morning and ketone levels <0.1 mmol/L with rare exceptions. The patient took a protein-rich bedtime snack or alternatively 30 g of uncooked corn starch. No severe hypoglycemias occurred throughout pregnancy (lowest documented glucose level 3.7 mmol/L), however, no conctinuos glucose monitoring was performed. In compliance with our recommendation, no oral glucose tolerance test was performed in the second trimester. Weight gain during pregnancy was 25 kg (weight before pregnancy 100 kg, BMI 34.6 kg/m^2). In the 37th week of gestation, she spontaneously delivered a healthy baby boy

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(weight 3400 g (76th centile), length 52 cm (71th centile), head circumference 32.5 cm (6th centile)). Management in the peripartal period included an intravenous glucose-electrolyte infusion (starting dose 10 g glucose/h), and regular blood glucose and ketone measurements in the mother during labour. Under this regimen, blood glucose remained stable throughout delivery. The boy could be breastfed without any problems and shows normal development at age 5 months. With him being a heterozygous carrier of the disease, no special precautions needed to be taken.

3. Discussion

GSD VI is a rare disorder with only about 50 cases reported. Due to the rather benign character and good prognosis of the disease, more and more patients will reach child-bearing age. To our knowledge, this is the first pregnancy of a woman with GSD VI.

To ensure an adequate supply of nutrients and energy to the unborn foetus, several alterations in maternal physiology occur during pregnancy mainly influenced by placental hormones [5]. While the first half of pregnancy is an anabolic state associated with increased insulin sensitivity and fat deposition in adipose tissue, the second half is characterized by a maternal insulin resistant state in order to preserve maternal glucose for foetal metabolism. Additionally, hepatic glucose production increases to meet the growing demands of both the foetus and the mother [6]. As women with GSD VI may not be able to match glucose production with increasing energy demands, patients with GSD VI are at risk for metabolic derangements with more pronounced hypoglycemia and hyperketonemia during pregnancy [7]. Careful monitoring and optimal dietetic treatment are therefore necessary throughout pregnancy to maintain maternal blood glucose levels in the normal range for the safety and proper development of the fetus [8]. For GSD type I, it has been shown that good metabolic control before conception and throughout pregnancy is directly related to successful outcomes [8]. In patients with GSD III it has been shown that maternal hypoglycemia may be associated with intrauterine growth restriction and low birth weight [7], and similar relations can be expected in GSD VI. The mainstay of therapy in GSD VI is the prevention of prolonged fasting, a protein-rich diet and supplementation with uncooked corn starch, if necessary. Treatment and monitoring have to be adapted on an individual basis. In the non-GSD population, oral glucose tolerance tests are routinely performed in the second trimester to screen for gestational diabetes. It is important to note that this test is contraindicated in women with GSDs, as fasting prior to the ingestion of 75 g of concentrated glucose is required for proper interpretation [8]. Fasting, however, poses a high risk of hypoglycemia on pregnant GSD women, and a large bolus of concentrated glucose can cause metabolic instability and result in lactic acidosis [8,9]. To prevent hypoglycemia during delivery, peripartum management should include administration of a high glucose-electrolyte infusion and regular monitoring of blood glucose and ketones during labour. Optimal planning and interdisciplinary collaboration between metabolic physicians and gynecologists is necessary to guarantee a safe setting for mother and child.

4. Conclusions

Our case demonstrates that successful pregnancy is possible in GSD VI. Careful monitoring during pregnancy and delivery is necessary to minimize the risk of recurrent hypoglycemia for both mother and child.

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