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RESEARCH REPORT

Successful Management of Pregnancies in Patients with Inherited Disorders of Ketone Body Metabolism

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Abstract Patients with succinyl-CoA:3-oxoacid CoA transferase (SCOT) deficiency and 3-hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency are at increased risk of developing metabolic acidosis and hypoglycemia during pregnancy, delivery, and postpartum period. This can be fatal if not treated appropriately. Pregnancy in such patients should be managed in a specialist center by a multidisciplinary team including metabolic physician, high-risk obstetrician, and metabolic dietician. We report two pregnancies in women with SCOT deficiency and HMG-CoA lyase deficiency, which were successfully managed at this tertiary care center. The patient with SCOT deficiency had recurrent ketoacidosis due to severe nausea and vomiting requiring several hospital admissions during pregnancy, while the patient with HMG-CoA lyase deficiency remained metabolically stable. Both patients, nevertheless, had normal delivery of live-born infants and had uneventful postpartum period.

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Introduction

Ketone bodies – acetoacetate and 3-hydroxybutyrate are the main sources of energy to the brain during fasting. These are produced mainly in the liver mitochondria from fatty acids and certain amino acids such as leucine, by the enzymes 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A synthase and 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A lyase which also catalyzes leucine degradation. Ketone bodies are metabolized in the peripheral tissues into acetyl CoA which enters Krebs cycle for energy production. The rate-limiting enzyme for ketolysis is succinyl-coenzyme A:3-oxoacid coenzyme A transferase (SCOT) (Fukao et al. 2014). HMG-CoA lyase deficiency (OMIM 613898) results in an inherited defect of ketogenesis and leucine degradation, while SCOT deficiency (OMIM 245050) causes an inherited defect of ketolysis. These patients develop acute metabolic crisis during fasting, febrile illness, infection, vomiting, diarrhea, or excessive physical exertion. During metabolic decompensation, patients with HMG-CoA lyase deficiency present with hypoketotic hypoglycemia, metabolic acidosis, and hyperammonemia, while those with SCOT deficiency present with severe ketoacidosis (Fukao et al. 2014). HMG-CoA lyase deficiency is relatively common in Saudi Arabia with an incidence of 1:55,357 in screened newborns (Ozand et al. 1991; Alfadhel et al. 2017). This is attributable to high consanguinity rate and the tribal structure in this population.

Early diagnosis and appropriate treatment of these disorders usually result in good long-term outcome with many patients reaching adulthood and pursuing goals of adult life. Pregnancy in these patients, however, carries a clear risk as nausea, vomiting, reduced oral intake, or excessive exertion may predispose them to severe, life-threatening crisis with metabolic acidosis and hypoglycemia. There are very limited data in the literature on the

experience of managing these patients during pregnancy (Merron and Akhtar 2009; Langendonk et al. 2012; Pipitone et al. 2016). We report two successful pregnancies in women with SCOT deficiency and HMG-CoA lyase deficiency. We will discuss their management and the outcome of these pregnancies.

Case 1

A 19-year-old female with SCOT deficiency had recurrent episodes of ketoacidosis since the age of 2 years. The diagnosis was confirmed by molecular testing which revealed a previously reported homozygous mutation in *OXCT1* (c.1402C>T; p.R468C). She was on a protein-restricted, low-fat diet and L-carnitine supplements. The patient presented with severe nausea and vomiting at 6 weeks of gestation. She had ketoacidosis with serum bicarbonate level of 16 mmol/L. She was treated with intravenous 10% dextrose infusion in 0.45% saline with bicarbonate and potassium added in the infusion as required. Carnitine was initially given as intravenous injection (100 mg/kg body weight/day) as she could not tolerate medication or food orally. Her serum electrolytes and ammonia concentrations were monitored closely. She required ondansetron and later meclizine and metoclopramide for frequent vomiting. An ultrasound examination showed single viable fetus corresponding to dates. Maternal echocardiogram was unremarkable. She gradually improved over the next 3 weeks and started tolerating small, frequent, carbohydrate-rich, low-fat, mildly protein-restricted meals. She also had high-energy nutritional supplements (1–1.5 kcal/mL) orally as 100 mL every 3 h to provide 50–75% of her energy requirements. The patient was allowed 0.9 g/kg protein, with 15–23% fat in the diet, and was advised to use glucose polymers frequently during sick days and post vomiting. Since she lived in another town, a comprehensive antenatal care plan of her management including care during metabolic crisis and in labor as well as in the postpartum period was sent to her local physician. She had repeated admissions to the local hospital during rest of the pregnancy with excessive vomiting and ketoacidosis.

As her pregnancy advanced, the amount of daily protein intake was gradually increased to 1.3 g/kg daily with 30% calories from fat. She took carnitine as 100 mg/kg/day. Her complete blood count, renal profile, quantitative amino acids, prealbumin, zinc, selenium, and copper were monitored every month. She initially lost 4 kg in weight during the first trimester of pregnancy and then gradually gained 10 kg by 38 weeks of gestation. At 36 weeks gestation, an ultrasound examination for growth showed estimated fetal weight of 1.9 kg which was below fifth percentile for gestational age and confirmed intrauterine fetal growth restriction. She had elective induction of labor at 38.3 weeks gestation and delivered a female infant by normal vaginal delivery in our hospital. The baby's weight was 2.31 kg which was below third percentile for gestational age. During labor and delivery, she was given epidural anesthesia to avoid physiological stress of pain and received 10% dextrose in 0.45% saline with 20 mmol of bicarbonate in each liter of infusion, given at the rate of 80 mL/h. Carnitine was administered by intravenous injection as 100 mg/kg/day divided into 8 hourly doses. Serum electrolytes were monitored every 6 hourly during labor and then 12 hourly for next 48 h. Dextrose infusion with added sodium bicarbonate was continued for 24 h after delivery. She remained metabolically stable and breastfed her baby. She was discharged home three days after delivery.

Case 2

A 20-year-old female with HMG-CoA lyase deficiency was diagnosed at the age of 10 months when she presented with hypoglycemia and metabolic acidosis following gastroenteritis. She had homozygous mutation in *HMGCL* (c.122G>A; p.R41Q), a common pathogenic variant seen in Saudi patients. She was on a leucine-restricted diet, I-Valex-II (leucine-free protein supplement) and L-carnitine. She was a university student. There was no history of metabolic decompensation in the adult life. Although she had received prepregnancy counseling, she did not inform us about her pregnancy and attended an antenatal clinic at her local hospital. During her routine follow-up appointment in the metabolic clinic, she disclosed that she was 7 months pregnant. She had so far remained metabolically stable with uneventful pregnancy. Her blood test results showed hemoglobin of 94 g/L, serum bicarbonate 22 mmol/L, random blood glucose 4.4 mmol/L, and prealbumin level 140 mg/L (200–400). Plasma quantitative amino acid profile was unremarkable. The dose of carnitine was adjusted as 85 mg/kg/day. She continued on a leucine-restricted diet and restarted I-Valex-II which she had not been taking for the last 3 months since she ran out of stock. Her total protein intake was increased to 1.1 g/kg daily. She was advised to take glucose polymer (CarboCH) 96 g daily to meet her energy requirements. This patient was followed up in the high-risk pregnancy clinic for the remainder of her pregnancy. A month later, blood prealbumin levels improved to 250 mg/L, with normal amino acid levels, and hemoglobin was 104 g/L. She remained metabolically stable and gained

the desired 12.9 kg in weight by 38 weeks of pregnancy (prepregnancy BMI 16.2 kg/m^2). Her detailed care plan of management during pregnancy, labor, and postpartum period was made available in her electronic hospital records for easy access by the multidisciplinary team. She was electively induced at 38 week and 3 days of gestation. During labor she received 10% dextrose in 0.45% saline infusion with 20 mmol of sodium bicarbonate added to each liter and intravenous carnitine injections as in Case 1. She also received elective epidural anesthesia during labor. She delivered a healthy male infant by normal vaginal delivery. The baby's weight was 2.76 kg, at tenth percentile for the gestational age. The patient's blood electrolytes, ammonia, and glucose levels were monitored closely during labor and in the postpartum period as in Case 1. She remained well and was discharged home on the third day of delivery.

Discussion

These cases highlight the potential risks involved with pregnancies in women with inherited disorders of ketone body metabolism such as SCOT deficiency and HMG-CoA lyase deficiency. Nausea and vomiting of pregnancy cause problems in maintaining adequate caloric intake and compliance to medication. This may lead to severe metabolic decompensation in these patients, which, if not treated adequately, could lead to maternal and fetal loss (Langendonk et al. 2012). Such patients require prepregnancy counseling and preferably should have planned pregnancy, managed at the specialist center.

To date, there is only one published case report of pregnancy in a patient with SCOT deficiency who required hospitalization twice during pregnancy; however, labor and postpartum period were uneventful (Merron and Akhtar 2009). Pregnant women are known to have relative insulin resistance and demonstrate much higher blood levels of free fatty acids and β-hydroxybutyrate after fasting compared with nonpregnant women (Metzger et al. 1982). Starvation may precipitate ketoacidosis in pregnant women (Frise et al. 2013). Pregnant patients with SCOT deficiency are, therefore, at much higher risk of developing severe ketoacidosis even with mild nausea which restricts caloric intake. Ketone bodies readily cross the placenta and may harm the fetus in the presence of acidosis and dehydration. Our patient with SCOT deficiency had a history of frequent episodes of ketoacidosis during childhood and adolescence. She subsequently had a stormy course throughout her pregnancy with excessive nausea and vomiting culminating in several admissions to her local hospital with severe ketoacidosis. The patient was successfully managed during these episodes in collaboration with her local physician. She, however, remained metabolically stable during the peripartum period.

The second case, a patient with HMG-CoA lyase deficiency is the first case report of an essentially uneventful pregnancy in a woman with this disorder, who successfully delivered a healthy boy. She remained metabolically stable and had no complications during pregnancy, labor, or postpartum. In the previously reported four pregnancies in two women with HMG-CoA lyase deficiency (Langendonk et al. 2012), there were two intrauterine fetal deaths, one termination of gestation and one maternal death. Although nausea and vomiting have been reported earlier as a specific problem in pregnancies with this particular disorder, our patient had minimal nausea and vomiting in early pregnancy which she tolerated very well without developing metabolic crisis.

Our patient with SCOT deficiency could not take adequate amount of calories and proteins due to intractable nausea and vomiting during most of her pregnancy. This, in addition to recurrent metabolic decompensations, led to the intrauterine fetal growth restriction. By contrast, fetal growth was not compromised in the patient with HMG-CoA lyase deficiency who managed to take her daily protein allowance and caloric requirement. Metabolic dieticians had regular telephonic contact with these patients and their nutritional requirements were constantly reviewed and modified with advancing pregnancy. The dose of carnitine was also adjusted as the pregnancy advanced. Both patients were followed up in the high-risk pregnancy clinic by obstetricians, in close collaboration with metabolic physicians and metabolic dieticians. They had elective induction of labor at around 38 weeks of gestation. Blood glucose, electrolytes, and ammonia levels were monitored closely during labor and after delivery. Prolonged high-dose oxytocin infusion was avoided as it may cause dilutional hyponatremia due to its antidiuretic effect. Pipitone et al. recently reported pregnancy in a patient with HMG-CoA lyase deficiency who developed metabolic acidosis due to overexertion during delivery (Pipitone et al. 2016). Our patients received elective epidural anesthesia in labor which saved them from physical stress and any related complication.

In summary management of these patients during pregnancy and delivery includes adequate caloric and protein intake with maintenance of hydration, electrolyte balance, and minimizing physiological stress of labor by giving epidural analgesia. The successful outcome in these two cases also reflects the importance of good collaboration in the multidisciplinary team, with a specific care plan in place preferably in the electronic patient record, to carefully

monitor and manage these patients during pregnancy, labor, and postpartum for a successful outcome.

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Synopsis

Successful management of pregnancy and delivery in these patients includes multidisciplinary approach with maintenance of adequate caloric and protein intake, hydration, electrolyte balance, and minimizing physiological stress.

Details of the Contributions of Individual Authors

RAS, MN, and ZNH devised the prenatal and perinatal management protocol.

RAS participated in the management of both patients, planned, and wrote the manuscript.

ZNH, MN, RK, BSH, and MA participated in the management of patients and contributed to the manuscript.

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RAS, MN, RK, BSH, MA, and ZNH declare that they do not have any competing interest.

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Informed consent has been taken from the patients.

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