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Ornithine transcarbamylase deficiency and pregnancy: A case series and review of recommendations

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A B S T R A C T

Background: Ornithine transcarbamylase deficiency (OTCD) is a rare disorder of the urea cycle that obstetricians should be aware of in order to guide management for pregnant carriers of the X-linked gene that causes the condition.
Cases: We present the pregnancy management and outcomes of two women with OTCD. The particular manifestations of the disease drive antenatal, intrapartum and postpartum management.
Conclusion: Preconception counseling, early prenatal diagnostics and multidisciplinary intrapartum and postpartum management plans contribute to improved outcomes for patients.

1. Introduction

Ornithine transcarbamylase deficiency (OTCD) is a rare disorder of the urea cycle caused by a deficiency of the mitochondrial enzyme ornithine transcarbamylase (OTC), which is expressed in the liver and small intestine [1]. The urea cycle is the process by which the body converts neurotoxic ammonia, formed from the breakdown of proteins (nitrogen), into urea, which is excreted [2,3]. OTCD is the only X-linked urea cycle disorder and is the most common enzymatic deficiency in the urea cycle, with an estimated incidence of 1: 14,000 births [4,5]. Due to X-linked inheritance, males are more severely affected than females and generally present with severe and often fatal hyperammonemia as neonates [2,4]. In women, the OTC gene undergoes X-inactivation, allowing for phenotypic variation based on the proportion of hepatocytes that have the mutant OTC gene on their active X chromosome [2,4,6]. While about 85% of female carriers are asymptomatic, some experience recurrent episodes of hyperammonemia, neurologic compromise, psychiatric symptoms, and gastrointestinal symptoms [3,6]. Symptomatic carriers often have a lifelong history of migraines, recurrent vomiting, abnormal behavior characterized by disorientation and confusion, anorexia, and self-avoidance of a high-protein diet [4].

It is important for obstetricians to be aware of this rare disease when managing and counseling female patients who are carriers. Heterozygous females have a 50% chance of passing the disease to their offspring [3]. Female carriers are at risk of pregnancy complications, as both the intrapartum and postpartum periods are catabolic states, possibly triggering hyperammonemia, which can cause life-threatening encephalopathy [2,3]. We present the pregnancy course and management of two patients with variable clinical manifestations of OTCD.

2. Case 1

This 33-year-old African American woman, G4P0121, had a significant medical history of OTCD, mild intermittent asthma, seizure disorder and chronic abdominal pain. She had been diagnosed with OTCD in childhood and had been admitted to hospital many times throughout her life for hyperammonemia, presenting with symptoms of altered mental status, nausea, vomiting and abdominal pain. Her obstetrical history was significant for an elective termination of pregnancy followed by a spontaneous vaginal delivery at 36 weeks after induction of labor for preterm prelabor rupture of membranes of a female infant known to be a carrier for OTCD. The patient's third pregnancy was a right tubal ectopic pregnancy for which she underwent laparoscopic right salpingectomy. During this pregnancy, at 7 weeks of gestation by LMP, the patient was seen in the emergency room for severe abdominal pain with no evidence of intrauterine gestation. Due to her recent history of an ectopic pregnancy, her worsening abdominal pain compared to her baseline pain associated with her OTCD, and no intrauterine gestation visible on transvaginal ultrasound, the patient underwent diagnostic laparoscopy to rule out an ectopic pregnancy. Laparoscopy did not reveal any

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abnormal findings, and after serial BHCG levels and ultrasound, an intrauterine pregnancy was confirmed at approximately 8 weeks of gestation.

The patient was cared for by maternal fetal medicine and pediatric metabolic specialists. She had been taking glycerol phenylbutyrate to prevent hyperammonemia prior to pregnancy, and this was continued. Shortly after her first prenatal visit, the patient was admitted to the hospital at 8 weeks of gestation with altered mental status and an ammonia level of 94 umol/L (reference range 11 to 51 μmol/L). The patient underwent cell-free DNA testing at 10 weeks of gestation, and the result was reported as 46 XX. Amniocentesis was offered as a definitive diagnostic test since cell-free DNA testing is a screening test; however, the patient declined. Her pregnancy was complicated by influenza B at 29 weeks, requiring admission. Her ammonia levels remained stable until 30 weeks of gestation, when she was readmitted with nausea and vomiting and found to have ammonia levels above 90 μmol/L and elevated liver function tests. She was diagnosed with cholestasis of pregnancy on this admission, with bile acids of 61 μmol/L (reference range 4.7–24.5 μmol/L), and started on ursodiol 300 mg BID once ammonia levels stabilized. At 33 weeks of gestation, preterm prelabor rupture of membranes occurred. Ammonia levels were obtained on admission and every 8 h intrapartum. The patient received 8 g of 10% arginine HCl in 1000 mL of 10% dextrose in water over 24 h with maintenance fluids of 10% dextrose in normal saline at 125 cc/h. If the patient was found to be in a prolonged catabolic state, there were measures in place for her to receive intralipids at 2 mL/kg, carnitine 250 mL every 6 h, and if her ammonia level was >130 she would receive a loading dose of 8 g 10% arginine HCl in 750 mL of 10% dextrose over a 2-h period. Serum glucose was monitored every 4 h in latent labor and ever 2 h in active labor; if glucose reached >120, insulin would be started. She did not receive betamethasone prior to delivery. Labor was augmented with oxytocin and she delivered a female infant weighing 2150 g, with Apgar scores of 8 and 8 at 1 and 5 min, respectively. Ammonia levels were stable throughout labor and delivery. Ammonia levels were checked every 8 h on postpartum day 1 and again prior to discharge on postpartum day 2. They remained stable throughout her postpartum course, and she was discharged on postpartum day 2. She later had an interval postpartum laparoscopic bilateral salpingectomy for sterilization.

3. Case 2

This 28-year-old African American woman, G4P1021, had a past medical history significant for OTCD and mild intermittent asthma. She had been diagnosed with OTCD in childhood and had had multiple hospital admissions outside of pregnancy for hyperammonemia presenting with altered mental status or nausea and vomiting. Her obstetrical history was significant for a vaginal delivery of a female infant negative for OTCD. Her second and third pregnancies had been terminated because in both the fetus was an affected male, diagnosed by amniocentesis.

She presented for this pregnancy at 19 weeks of gestation. The patient was counseled on screening cell-free DNA testing vs immediate amniocentesis and she chose amniocentesis. This was performed and an female unaffected with OTCD was confirmed. The patient's OTCD was managed by a low-protein diet and her ammonia levels were monitored during her antenatal course. The delivery plan made by metabolic genetics and maternal fetal medicine included complete metabolic panel and ammonia level testing on admission followed by testing for ammonia levels every 12 h intrapartum. The patient was started on maintenance fluids of 10% dextrose in normal saline at 125 cc/h.

She presented at 38 weeks to labor and delivery complaining of contractions. She was admitted in active labor and delivered a female infant weighing 2914 g, with Apgar scores of 9 and 9 at 1 and 5 min, respectively. The patient was put on a low-protein diet of 35 g/day after delivery. On postpartum day 1, she underwent tubal sterilization, as desired. Her ammonia levels were monitored postpartum, and she did not require any interventions. She was followed up by the high-risk obstetrics service and did not require medications to manage her OTCD postpartum.

4. Discussion

As evident from these cases, clinical presentation and severity of disease of OTCD are variable. The patient in case 1 was generally more symptomatic in and outside of pregnancy compared to the patient described in case 2. A multidisciplinary team of obstetrics, maternal fetal medicine, metabolic genetics and nutrition is recommended. Patients should be counseled on the potential complications of pregnancy with OTCD, the possible outcomes based on fetal sex and the benefits of early prenatal diagnosis by chorionic villous sampling (CVS) or amniocentesis [4]. Preconception counseling for known carrier females is favored over counseling after conception, especially if there have been previous pregnancies with affected male fetuses [7]. Counseling should focus on outcomes for affected male versus female infants since OTCD is particularly severe in hemizygous males [8]. A study by Torkzaban et al. of neonatal outcomes showed that liver transplant was reported in 13.6% of male neonates and death in 12.5% [3]. This differs from affected female infants, of whom 66% are generally asymptomatic and can appear normal until factors such as high protein intake, trauma, infections, surgery, pregnancy, or other physiological stress precipitate symptoms [1]. If neonatal-onset OTCD is diagnosed by CVS or amniocentesis prenatally, intravenous treatment with ammonia scavengers within a few hours of birth can help prevent hyperammonemia and coma [6].

As stated, some female carriers do not present with symptoms until pregnancy. Unless diagnosed after birth, it can be difficult to diagnose OTCD in females because symptoms such as vomiting, migraines and confusion or altered mental status can occur with many other pathologies [9]. OTCD should be considered in women with unexplained coma, signs of cerebral edema, respiratory alkalosis with hyperventilation (pathognomonic), recurrent vomiting, lethargy, abnormal behavior, ataxia and a history of selective anorexia (especially for high-protein foods) [1,2,6].

Management of known OTCD carrier females in pregnancy is similar in the antepartum, intrapartum and postpartum periods and focuses on preventing hyperammonemic crises. The antepartum period is generally less plagued by symptomatic episodes of hyperammonemia because of increased nitrogen demands of the placenta, uterus, and fetus [1,2]. When patients first present for care, baseline ammonia level and amino acid levels should be determined, with regular prenatal labs [4]. Management in the antepartum period mainly focuses on avoidance of triggers, nutritional control with a low-protein diet and medications that promote the excretion of nitrogen [2–4]. Normal adult ammonia levels should be less than 50 umol/L, so nitrogen-scavenging medications should be started with patients whose levels are persistently above this value [3]. Nitrogen-scavenger medications that are commonly used for long-term maintenance therapy are glycerol phenylbutyrate and sodium benzoate [6].

When patients present very early in pregnancy, such as case 1 above, it can be difficult to differentiate symptoms associated with known OTCD from other etiologies. Thus, physicians should take a detailed history and perform a thorough workup, including checking ammonia levels to assess for hyperammonemia and exacerbation of OTCD, along with assessing other pertinent labs/imaging tests to rule out differential diagnoses. For instance, it was considered important to rule out an emergency such as ectopic pregnancy in this patient as her pain was reported to be worse than at baseline, she had a positive quantitative pregnancy test with no intrauterine pregnancy evident on transvaginal ultrasound, and a history of prior ectopic pregnancy. All emergent diagnoses should be ruled out in pregnancy before associating symptoms with an OTCD exacerbation.

Nausea and vomiting of pregnancy, a common issue in the first

trimester, is a particular concern with OTCD and should be aggressively prevented since persistent vomiting and dehydration will trigger hyperammonemia [2]. One study found that all patients with OTCD who were symptomatic presented with lethargy, vomiting and irritability, which can be confused with normal nausea and vomiting of pregnancy [10]. Some sources recommend serial growth scans to monitor for fetal growth restriction due to patients' low-protein diet [2]. Since there is little information on the impact of maternal or fetal OTCD on fetal well-being, it has been suggested that weekly antenatal surveillance begin at 32 weeks of gestation [4]. It should also be discussed with the patient that if preterm labor occurs, corticosteroid use is not recommended in OTCD as it can trigger a catabolic state [3,6].

A labor plan should be decided upon early to prevent issues surrounding management intrapartum. All patients with OTCD should be offered a vaginal delivery unless contraindicated by other maternal or fetal indications. Labor is a catabolic state and causes increased energy requirements, so it is important to prevent prolonged labor, ensure adequate hydration and caloric intake, and have anti-emetics ordered in case of vomiting [2]. Several sources recommend checking ammonia levels every 6 h intrapartum and using fluids with 10% dextrose to substitute for caloric intake [3,4,11]. Glucose levels should be monitored, and insulin administered if blood glucose levels are above 100 mg/dL [4]. Neuraxial anesthesia reduces catabolism and the hypothalamic pituitary response to surgical stress and decreases maternal stress hormones during labor, thus it is recommended that patients consider an early epidural [1]. Close monitoring of vital signs intrapartum, especially blood pressure, is required because symptomatic patients can develop tonic-clonic seizures, which must be differentiated from eclampsia [4]. For patients undergoing scheduled cesarean delivery for other obstetrical indications, overnight fasting can trigger hyperammonemia so it is recommended to admit these patients the night prior to their scheduled delivery and administer intravenous hydration with 5% or 10% dextrose [4].

If an acute intrapartum episode of hyperammonemia occurs, protein intake must be stopped and nutrition should be provided with 10% dextrose, preventing further protein breakdown and ammonia accumulation. Additional infusion of intralipid therapy can provide extra calories; however, complete protein restriction should be limited to 24–48 h as depletion of amino acids will trigger protein catabolism. If the plasma ammonia concentration approaches three times normal, arginine, sodium benzoate and sodium phenylbutyrate should be administered [1]. It has been recommended to start oral sodium benzoate at 5 g/m^2/day split into three doses or an intravenous infusion of Ammonul at 5.5 g/m^2/day if oral supplementation can't be tolerated along with IV arginine [4]. Ammonul is an intravenous nitrogen-scavenger therapy made up of a mixture of sodium phenylacetate and sodium benzoate for acute management of hyperammonemia and has not shown any deleterious effects in mothers or newborns after use intrapartum [6,8]. In OTCD citrulline is not synthesized, resulting in decreased production of arginine, which is further worsened by fasting in labor and thus citrulline supplementation may be necessary [1,4]. If ammonia levels are not decreasing within 8 h of treatment, or if there has been an acute rise to levels of 250 mg/dL, hemodialysis should be started [4].

The postpartum period is the most critical time to monitor for signs of hyperammonemia. It is hypothesized that the combination of the removal of the nitrogen-consuming fetal–placental unit along with involution of the uterus, which releases excess nitrogen, causes an increase in nitrogen levels, triggering hyperammonemia [2,4,11,12]. Generally, hyperammonemia and decompensation will occur 2–14 days postpartum but can occur for up to 6–8 weeks and must be recognized in order to prevent irreversible coma and death [2,3]. While still hospitalized postpartum, patients should continue to have their ammonia levels trended, be counseled on the signs and symptoms of hyperammonemia and should be seen within 1 week of discharge [1,3]. Symptoms of hyperammonemia can mimic postpartum depression and psychosis if patients present with irritation and altered mental status and must be differentiated [12]. Patients should be counseled that breastfeeding increases energy demands and therefore adequate calorie intake must occur to prevent hyperammonemia [2].

Contributors

Gabriella Pinho is the primary author, conducted the literature search, wrote up case 1 and most of the introduction and discussion, and wrote revisions.

Gabriela Ross assisted with literature search, wrote case 2, and assisted in writing the introduction and discussion.

Kaila Krishnamoorthy contributed to the revisions and edits.

Christina Kresge contributed to patient management from a metabolic specialist standpoint, and to the revisions and edits.

Ling Yu Shih contributed to patient management from a metabolic specialist standpoint, and to the revisions and edits.

Joseph J. Apuzzio contributed to contributed to patient management from an MFM specialist standpoint, and to the revisions and edits.

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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