Molecular Genetics and Metabolism Reports 33 (2022) 100894

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

# Considerations for prenatal and postpartum management of a female patient with ornithine transcarbamylase deficiency☆

Annette Feigenbaum [a,*], Leah Lamale-Smith [b], Lawrence Weinstein [c]

[a] Department of Pediatrics and Biochemical Genetics, Rady Children's Hospital-San Diego, University of California San Diego, 3020 Children's Way #5031, San Diego, CA 92123, USA
[b] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Diego, 9300 Campus Point Drive, #7433, San Diego, CA 92037, USA
[c] Department of Anesthesiology, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA

ARTICLE INFO

*Keywords*
Urea cycle disorder
Ornithine transcarbamylase deficiency
X-linked, hyperammonemia
Peripartum management
Pregnancy

ABSTRACT

We report on pregnancy management and outcomes in a 27-year-old female patient with ornithine transcarbamylase (OTC) deficiency, the most common inherited enzyme deficiency in the urea cycle. Our patient was diagnosed during childhood after hyperammonemia associated with surgery and steroid treatment and was well-controlled with nitrogen scavenger treatment, low-protein diet, and L-citrulline supplementation. *OTC* gene sequencing identified a variant of unknown significance that has more recently been classified as likely pathogenic. Women with OTC deficiency are at increased risk of hyperammonemia during pregnancy and the postpartum period, therefore monthly follow up and laboratory assessments are critical in management decision making. Our patient was maintained on glycerol phenylbutyrate, L-citrulline and essential amino acid supplements, along with restricted protein intake during pregnancy. A multidisciplinary approach with the obstetrics, prenatal genetics, high risk obstetric, and anesthesia teams was also necessary for optimal management during pregnancy, throughout labor and delivery, and during the postpartum period. After successful childbirth and discharge, our patient experienced a hyperammonemic crisis related to poor enteral nutrition, and acute management protocols were implemented to stabilize her. For her newborn son, acute hyperammonemia protocols were on standby, and newborn screening and laboratory testing were expedited to assess his risk. He was healthy and did not experience symptoms of concern. In this case report, we emphasize the importance of close collaboration with maternal-fetal medicine team members during and immediately after pregnancy to ensure successful management of a female patient with OTC deficiency and her newborn.

## 1. Introduction

Ornithine transcarbamylase (OTC) deficiency, the most common defect in the urea cycle, is caused by mutations in the *OTC* gene (*OTC*; OMIM 300461) on chromosome Xp11.4 [1,2]. It follows a pattern of X-linked inheritance and most commonly presents as either severe neonatal-onset disease in males or as late-onset disease in either sex [1,2]. Males with severe neonatal-onset OTC deficiency are typically diagnosed symptomatically within the first week of life [2]. Conversely, males and heterozygous females with later-onset disease may have a wide spectrum of phenotypes, depending on the severity of the enzyme deficiency and X-chromosome inactivation pattern, and can present at any time during infancy to late adulthood [2]. Although the estimated incidence of OTC deficiency is 1 in 56,600 live births in the United States, it is likely that the actual prevalence may be underestimated due to misdiagnosed or underrecognized oligosymptomatic patients [1].

Patients with OTC deficiency can be diagnosed through clinical and laboratory findings and/or genetic testing. Newborn screening tests measuring citrulline or other biochemical markers have historically been ineffective at identifying patients with OTC deficiency due to poor specificity and sensitivity [3]. Additionally, commercially available genetic testing platforms may not all have the specificity to identify

*Abbreviations:* BCAA, branched-chain amino acids; BID, twice daily; D10, 10% dextrose; EAA, essential amino acids; GPB, glycerol phenylbutyrate; IV, intravenous; NICU, neonatal intensive care unit; OTC, ornithine transcarbamylase; PICC, peripherally inserted central catheter; PO, per os/orally; TID, three times daily; UCD, urea cycle disorder.

☆ This paper is part of a supplement supported by Horizon Therapeutics.

* Corresponding author at: 3020 Children's Way #5031, San Diego, CA 92123, USA.
*E-mail addresses:* afeigenbaum@health.ucsd.edu (A. Feigenbaum), llamalesmith@ucsd.edu (L. Lamale-Smith), lsweinstein@ucsd.edu (L. Weinstein).

https://doi.org/10.1016/j.ymgmr.2022.100894
Received 13 May 2022; Received in revised form 27 June 2022; Accepted 27 June 2022
Available online 12 July 2022

novel pathogenic variants and may contribute to underdiagnosis [4]. Increased availability and recent advances in genome sequencing have allowed for better identification of potentially pathogenic variants and may facilitate faster diagnosis of presymptomatic patients [3]. Missense, nonsense, and splice site variants; small intragenic deletions/insertions; single exon, multiexon, or whole-gene deletions/duplications; and promoter and enhancer mutations have been identified through sequence analysis of the *OTC* gene. For example, a deep intronic pathogenic variant has been described, suggesting that other undiscovered mutations may exist in patients with no previously identified disease-causative *OTC* mutations [2,4,5].

Common symptoms associated with urea cycle disorders (UCDs) include hyperammonemia, hepatic dysfunction, and various neuropsychologic complications [6–8]. Heterozygous female patients with OTC deficiency, commonly referred to as "carriers", do not have a complete loss of function and may have less severe symptoms than patients with a complete loss of enzyme function [2,9]. Nonetheless, heterozygous females often present with nonspecific symptoms such as protein intolerance, cyclic vomiting, headache, altered mental status, and neurologic deficiencies arising from elevated ammonia, which contribute to significant morbidity and mortality [1,10]. Prompt diagnosis and treatment are therefore essential to limit the long-term sequelae of elevated ammonia. The foundation of management for patients with UCDs, including female heterozygotes with OTC deficiency, is based on a combination of low-protein diet, amino acid supplementation, and nitrogen scavenger treatment or liver transplant to regulate ammonia and glutamine levels [8]. Investigational therapeutic options, including liver cell transplant, protein or mRNA therapy, and gene editing/therapy may also be considered [8,11].

The management of heterozygous female patients with OTC deficiency is generally tailored based on disease severity and risk for decompensation. Triggers for hyperammonemia include infection, fever, fasting, surgery, or the increased metabolic demands of pregnancy [6,8]. Although some patients are adequately managed through low-protein diet and supplements, others may also require ongoing treatment with nitrogen scavengers [6]. Previously well-controlled patients are at increased risk for metabolic stress and catabolism during pregnancy due to insufficient calorie intake, changes in metabolic rate, and increased protein and micronutrient requirements in each trimester [8,12–14]. Additional catabolic stress in the peri-, ante-, and postnatal periods (eg, labor, surgery/caesarian section, uterine involution after birth, infection, breastfeeding demands) can lead to hyperammonemia [12,15–19]. Furthermore, psychiatric manifestations stemming from hyperammonemia may be misdiagnosed as pregnancy-related or postpartum psychosis [19]. Therefore, a well-established labor management plan, including frequent ammonia monitoring and recommendations for intrapartum intravenous fluid replacement for caloric and nutritional needs, is necessary to prevent poor outcomes in pregnant women with OTC deficiency [17–20]. Here, we report on an adult heterozygous female patient with late-onset OTC deficiency who was diagnosed during childhood and describe our approach to developing a tailored management regimen for her during her pregnancy.

## 2. Case presentation

### 2.1. Patient report/history

This is a report of pregnancy management in a 27-year-old woman with OTC deficiency. Our patient was diagnosed at 12 years of age when she experienced a hyperammonemic crisis triggered by thoracic spinal fusion for thoracolumbar scoliosis and steroid treatment. At diagnosis, genetic analysis in a research laboratory reported a variant of unknown significance (c.539A > C, p.Q180P; NM_000531.6), a missense mutation that has since been classified as likely pathogenic. Molecular testing on the patient's mother confirmed that she did not carry this variant. It is unclear whether expanded family genetic screening was performed, and there was no family history suggestive of disease.

After diagnosis, our patient was managed with a protein restricted diet, oral sodium benzoate (3 g/day three times daily [TID]), and L-citrulline supplementation. Although she did not experience additional hyperammonemic crises during adolescence, elevated glutamine was reported (peak 1646 μmol/L, reference range, 205–756 μmol/L). She transferred to our institution for management at 24 years of age. Initial laboratory monitoring showed elevated glutamine at 822 μmol/L and mildly elevated ammonia at 43 μmol/L (reference range, 9–33 μmol/L). Our patient continued treatment with sodium benzoate (3.2 g/day) and supplementation with L-citrulline (6 g/day), multivitamins, calcium, and vitamin D. She attempted to adhere to a recommended low protein diet targeting 45–50 g/day but was only consuming an average of 0.35 g/kg/day of intact protein (22.5 g/day). Routine laboratory monitoring was conducted every 3 months.

When she was 26 years of age, we switched our patient from sodium benzoate treatment to glycerol phenylbutyrate (GPB) treatment (3 mL TID titrated to 5 mL TID [8.1 mL/m$^2$]) after she reported worsening headaches and quarterly laboratory monitoring showed glutamine level elevations (902 μmol/L). She also had borderline low vitamin B12 levels (263 pg/mL; reference range, 190–950 pg/mL) and low carnitine levels (free carnitine 9–11 μmol/L; reference range, >20 μmol/L). We recommended that our patient increase her daily total dietary protein allowance to at least 0.85 g/kg and start carnitine supplementation. Although we also recommended essential ammino acid (EAA) supplementation, it was taken inconsistently due to insurance denial and financial constraints. Nonetheless, our patient remained stable on this regimen, felt well, and experienced no hospitalizations.

### 2.2. Pregnancy management

At 27 years of age, our patient reported pregnancy at 8 weeks of gestation. She had initially stopped taking her medications due to concern for teratogenicity, resulting in elevated glutamine at 1145 μmol/L. After discussion, she restarted GPB (5 mL TID), and her glutamine levels normalized. Supplementation with EAA (providing 20 g of protein equivalent per day; total protein intake ±1 g/kg/day) and increased dosage of L-citrulline (9.6 g twice daily [BID]) were prescribed. GPB dosage was not altered during the pregnancy and phenylbutyrate metabolite testing confirmed therapeutic drug dosing and no toxicity.

Our patient had significant anxiety regarding her child's risk of inheriting OTC deficiency. She underwent noninvasive prenatal testing at 13 weeks gestation, which predicted a male fetus (99.4% accuracy). Based on concerns for potentially severe neonatal symptoms in an affected child, the patient decided to undergo additional prenatal testing by amniocentesis that showed the baby did not carry the same variant as our patient. This additional testing, along with extensive discussions with our team and genetic counselor, helped to reassure our patient. However, full sequencing of the *OTC* gene was not performed on mother or fetus and, thus, the possibility of another pathologic variant being present could not be excluded.

Monthly laboratory testing during pregnancy assessed amino acid, ammonia, glutamine, liver function, carnitine, branched-chain amino acid (BCAA), prealbumin, and citrulline levels. Pre-labor ammonia levels were well-controlled (Fig. 1), and no changes were made to our patient's daily recommended protein allowances. Our patient is a dietitian and remained well-informed and receptive to disease state education. Regular nutritional counseling was provided throughout her pregnancy; she kept a record of her dietary intake and was encouraged to meet her protein and calorie needs. Plasma amino acid levels change markedly during pregnancy and can vary based on several factors, including trimester stage. Leucine and valine have been noted to decrease early during pregnancy, while plasma isoleucine concentrations remain more stable [14,21]. Despite steps that our patient took to meet her protein and calorie needs, her BCAA levels remained lower

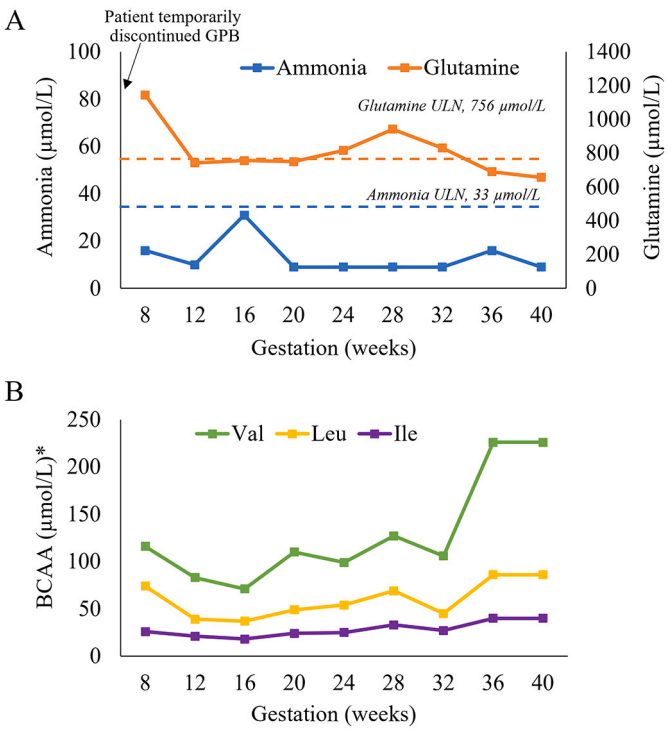


**Fig. 1.** Biochemical Testing During Pregnancy.
BCAA, branched-chain amino acid; GPB, glycerol phenylbutyrate; Ile, isoleucine; Leu, leucine; ULN, upper limit of normal; Val, valine.
Biomarkers (solid lines), limits of normal range (dashed lines).
A. Glutamine and ammonia levels. B. Branched-chain amino acid levels.
*Maternal BCAA levels change markedly during pregnancy and can vary based on several factors, including trimester stage.

than previously published overall normals (Fig. 1; [14]) and plasma carnitine dropped at 6 months of gestation. Her carnitine supplement dosage was increased, which normalized plasma carnitine. Unfortunately, midway through her pregnancy, the patient's insurance denied EAA coverage despite previous coverage, resulting in inconsistent amino acid supplement intake.

Given that many signs and symptoms of hyperammonemic crisis can be mistaken as common symptoms of pregnancy, the goals for pregnancy management included close collaboration and discussion with non-UCD specialists, including anesthesiologists, obstetricians, prenatal geneticists, and the high-risk obstetric unit. Full team discussions included considerations for labor and delivery (ie, caesarian vs vaginal delivery), anesthesia options (ie, general vs spinal anesthesia), and anticipated need for oral (PO) and intravenous (IV) nutrition and nitrogen scavenger therapy throughout labor and delivery and the postpartum period (Table 1). A scheduled vaginal delivery with epidural at 39 weeks of gestation was deemed possible, and a written plan was put in place at the delivery center prior to the scheduled delivery. An alternate plan was also put in place if our patient spontaneously labored prior to her planned induction.

### 2.3. Labor and delivery management and outcomes

As planned, our patient was admitted for controlled induction of labor at 39 weeks. A peripherally inserted central catheter (PICC) line was inserted as a precaution, and our patient was treated with oral GPB (5 mL TID), EAA, carnitine, L-citrulline, IV lipids, and 10% dextrose water with electrolytes (D10) during labor. IV carnitine, L-arginine, and sodium phenylacetate/sodium benzoate were on standby if needed. Throughout labor, we monitored ammonia levels every 6 to 8 h and assessed our patient for altered mental status or persistent vomiting. Our patient's ammonia levels remained well controlled during delivery, and she delivered a healthy male newborn vaginally (weight 3.66 kg; Apgar scores of 8 and 9 at 1 and 5 min, respectively).

### 2.4. Postpartum care and acute event management

Postpartum care recommendations, which were communicated to the extended care team via letters, emails, daily calls, and chart notes, included continuation of IV D10 with electrolytes and lipids until our patient was eating well. After her successful delivery, our patient's postpartum ammonia levels were initially well controlled, and she tolerated her low-protein diet and EAA. On postpartum day 1, she was doing well and was transitioned from IV D10 to D5 with electrolytes. After this change, our patient's ammonia levels rose to >100 µmol/L (peak, 136 µmol/L). *Re*-initiation of IV D10 and lipids, along with a vegan/minimal protein diet over the next 33 h normalized ammonia levels. IV fluids were discontinued on postpartum day 3, with continued improvements in ammonia levels and restart of a limited protein diet of <50 g/day.

Our patient was discharged from the hospital 4 days postdelivery with no other reported symptoms. However, on postdelivery days 7–11, our patient was readmitted due to poor food intake, nausea, and lightheadedness and was found to have elevated ammonia at 83 µmol/L. During this hospitalization, her ammonia levels rose and peaked at 147 µmol/L. She was treated with IV glucose and lipids (IV D10 normal saline, 4.5 L/day; IV intralipid 20%, 20 mL/h; IV carnitine, 750 mg every 6 h) and IV sodium phenylacetate/sodium benzoate (Fig. 2). After stabilization, treatment with GPB (5 mL TID), L-citrulline PO, EAA, and a limited protein diet (30 g/day of protein) was reinitiated, along with ondansetron as needed for nausea.

On discharge, we recommended that our patient consume a minimum of 2400 kcal/day to avoid catabolism, including 500 kcal/day derived from protein-free nutritional supplementation. She continues to adhere to a limited protein diet at up to 50 g/day and has continued supplementation with multivitamins, calcium, vitamin B12, and EAA. She was thereafter stable on her prepregnancy GPB dosage of 5 mL TID.

**Table 1**
Pregnancy management and monitoring plan.

| First Trimester | Second/Third Trimesters | Postpartum |
|---|---|---|
| Nausea management | Education and instruction regarding potential increases in protein and supplement needs | Early postpartum treatment and monitoring plan |
| Expanded care team and patient discussions about childbirth options | Adjusting dietary intake based on changing metabolic needs | Emergency management plans for newborn and patient on standby |
| Nutritional and genetic counseling | Serial fetal growth assessment with ultrasonography | Diet and medication options |
| Prenatal genetic testing | Monthly laboratory testing | Close contact for ≈8 weeks after delivery to monitor catabolism due to parturition |
| Monthly laboratory testing | Written management plans for labor and delivery, including use of epidural analgesia to manage pain/stress that could trigger possible acute metabolic decompensation<br>Clinician–patient discussions on breastfeeding | |

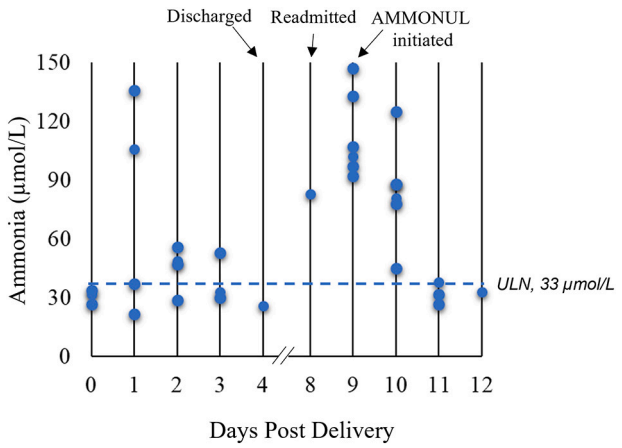


**Fig. 2.** Postpartum ammonia levels.
ULN, upper limit of normal.

### *2.5. Newborn monitoring and patient management plan*

There were no signs or symptoms of concern for our patient's son at birth; regardless, we recommended that the newborn remain inpatient during the first days of life for close laboratory and symptom monitoring. In conjunction with the neonatal intensive care unit (NICU)/pediatrics team, we recommended expedited routine newborn screening along with urine organic acid, orotic acid, and plasma amino acid testing at 24 h of age. Newborn screening at 18 h of life indicated normal citrulline (25 µmol/L; reference range, 10–45 µmol/L). Urine orotic acid was also normal (1.6 mmol/mol creatinine; reference range, 0–3 mmol/mol creatinine).

Because prenatal genetic testing results did not exclude the possibility of an undetected pathologic variant, and given the potential risk to an affected neonate, a plan was implemented to check the newborn's ammonia levels at birth if he was symptomatic (eg, feeding issues, lethargy) or every 8 h starting at 24 h of life if he remained without notable symptoms. Ammonia testing was to continue until day of life 3 or 4 or until plasma amino acid and urinary orotic acid testing results were obtained. The NICU was advised to immediately contact the metabolic team in the event of any abnormal laboratory testing or occurrence of encephalopathy. Peak ammonia level was 56 µmol/L at day 1 of life (reference range, <57 µmol/L), decreasing to 27 µmol/L by day 4 of life.

Because the newborn did not have any concerning symptoms, our patient was permitted to establish normal feeds through breastfeeding. There are insufficient data on the use of GPB during pregnancy and breastfeeding, and GPB is not recommended during breastfeeding per the drug label; however, after discussion, our team ultimately recommended that our patient continue her treatment with GPB. Treatment with this regimen during pregnancy and postpartum breastfeeding was uneventful. At his last follow-up at 11 months of age, our patient's son showed normal growth and development and remained asymptomatic with no other notable medical issues.

We also coordinated further genetic testing with full gene sequencing and deletion/duplication analyses for our patient. This confirmed the initial diagnostic testing but reclassified her variant as likely pathogenic.

## 3. Materials and methods

Medical records and clinical parameters were reviewed by the treating clinical team.

## 4. Discussion

We report on our management considerations for a heterozygous female patient with OTC deficiency at our institution during her pregnancy and the intrapartum and postpartum periods. There is limited consensus-based clinical guidance for the management of OTC deficiency during or after pregnancy, and management plans are generally tailored to the individual patient [16–18]. Patients with UCDs and other genetically inherited conditions should receive preconception counseling to clarify hereditary implications and facilitate decision making [2]. Although the immediate implications of X-linked diseases are greatest for affected male fetuses, determination of a female fetus during prenatal testing should not negate the importance of discussions regarding the risks of OTC deficiency in either sex, as hyperammonemic crises can be triggered by stressors at any age in females [2].

Advances in molecular testing enabling confirmation of suspected diagnoses, coupled with improved long-term management, have led to a greater number of patients surviving into adulthood and starting a family [18,19]. Clinical presentation and severity of symptoms in women with OTC are variable [2,16,18]. Our patient was diagnosed with late-onset OTC deficiency at 11 years of age, prior to which she had no episodes of hyperammonemia. Her OTC deficiency was likely unmasked due to a combination of factors, including metabolic stress related to surgery and steroid treatment [6,12,16]. Although her OTC deficiency was well-controlled with medical management following her diagnosis, her symptoms were later exacerbated by the metabolic demands of pregnancy. We reviewed available literature to develop a detailed multidisciplinary management plan, which was generally successful except for two episodes of postpartum hyperammonemia that may have been avoided through stricter adherence to nutritional recommendations and closer inpatient monitoring.

Advances in genome sequencing have allowed for improved identification of potentially pathogenic variants, which aided in identifying our patient's *OTC* mutation [3,4]. The identified missense *OTC* mutation replaces glutamine with proline in exon 5 of codon 180 to potentially disrupt the secondary structure of the OTC protein and has previously been noted in another patient [2,22]. Another *OTC* variant affecting the glutamine residue in the same codon (c.540G > C, p.Q180H; NM_00531.6) has been confirmed as pathogenic [23,24]. However, algorithms developed to predict the effect of our patient's variant are not conclusive, and there is currently no functional evidence for this mutation (NM_000531.6). Taken together, these observations suggest that our patient's variant is also disease causing.

Special nutritional considerations and additional protein intake may be needed for heterozygous women with OTC deficiency during each trimester of pregnancy and while breastfeeding. Furthermore, excessive catabolism is possible during the prenatal and postpartum periods [16,18–20,25,26]. The changing metabolic needs of women with OTC deficiency during pregnancy and the postpartum period underscore the critical need for close monitoring of metabolic status and protein consumption by a metabolic dietitian [17–20]. To avoid catabolism and metabolic decompensation, nitrogen scavenger treatment is recommended for patients with OTC deficiency during pregnancy and lactation if their disease cannot be managed with diet and/or amino acid supplementation alone [2,8]. Although there are insufficient data on the use of GPB during pregnancy and breastfeeding, our patient was well-maintained on GPB therapy during the peri-, ante-, and postnatal periods, including during lactation. Our patient's postpartum decompensation was not related to this therapy. Low BCAA levels have been reported with the use of phenylbutyrate, which together with dietary intake issues, may have contributed to her acute crisis. Despite this, the neonate was well grown and developed normally.

Preemptive management is possible in women whose OTC deficiency diagnoses are known prior to pregnancy. In these women, detailed pregnancy management and labor plans should be implemented early to address known triggers of hyperammonemia arising from the increased metabolic demands during each trimester and the peripartum period [16,17,19]. Despite proactive risk-mitigation protocols, including tailored patient education and engagement, the possibility of

hyperammonemia is greatest during the postpartum period due to rapid uterine involution and resulting protein breakdown in the days immediately following childbirth [16,18,19]. Our patient was hospitalized with hyperammonemia several days after giving birth (peak, 147 μmol/L), consistent with other published examples of postpartum decompensation in women with OTC deficiency (ammonia levels ranging from ≈100 to >250 μmol/L observed from postpartum days 3–14) [15,16,25–27].

Women with late-onset OTC deficiency whose initial crises are triggered by pregnancy have higher maternal morbidity and mortality than if they had been diagnosed prior to conception [16,28]. Furthermore, early identification of late-onset OTC deficiency and continuous metabolic control are critical because even mildly symptomatic patients can demonstrate cognitive defects that may impact their ability to adhere to management regimens [29,30]. Symptoms of hyperammonemia can be hidden by pregnancy-related issues, and nausea, vomiting, headaches, mood disturbances, and seizures can be misattributed to hormonal changes. Furthermore, mental status changes postpartum in women with OTC deficiency have been misdiagnosed as postpartum psychosis or depression [16]. Therefore, close communication, frequent multidisciplinary monitoring, and prompt treatment of metabolic decompensations are necessary to prevent poor outcomes in pregnant female patients with OTC deficiency [17–19,26,28]. Our patient confidently navigated management of her OTC deficiency concurrently during her pregnancy because she was already accustomed to adhering to her UCD treatment regimen and had a multidisciplinary team supporting her throughout her pregnancy.

## 5. Conclusion

In summary, this case study demonstrates management approaches for a pregnant adult female patient with late-onset OTC deficiency. She had a history of established adherence to her UCD management regimen prior to pregnancy and had reported few symptoms indicative of metabolic instability. Her pregnancy management was similar to her prepregnancy regimen and was guided by her biochemical profile. We emphasize the importance of improved diagnosis of female heterozygotes with OTC deficiency prior to pregnancy to allow preventative and preemptive management of both the mother and neonate. Our experience further underscores the importance of maintaining close collaboration with members of the maternal-fetal team during and immediately after pregnancy to ensure successful management of a female patient with OTC deficiency and her newborn.

## Consent for publication

Written informed consent was obtained from our patient for publication of this case report.

## Funding

Horizon Therapeutics plc funded manuscript editorial support, including editorial review, author coordination, and manuscript submission. The authors confirm independence from the sponsor; the content of the article has not been influenced by the sponsor. No authors received compensation for the preparation of this manuscript outside of normal employment obligations.

## Declaration of Competing Interest

A Feigenbaum has received honoraria from Horizon Therapeutics plc for consulting/advisory activities.

## Data availability

No data was used for the research described in the article.

## Acknowledgements

The authors wish to thank the patient and the reviewers of the paper. We are also grateful to our anesthesia, obstetric, pediatric, and genetic counselor colleagues. Thanks to Anisa Ismail, PhD, for assistance with medical writing and The Lockwood Group for editorial review, author coordination, and manuscript submission.

## References

[1] N. Ah Mew, K.L. Simpson, A.L. Gropman, B.C. Lanpher, K.A. Chapman, M. L. Summar, Urea cycle disorders overview, in: M.P. Adam, H.H. Ardinger, R. A. Pagon, S.E. Wallace (Eds.), GeneReviews® [Internet], University of Washington, Seattle, Seattle (WA), 2003 Apr 29 [Updated 2017 Jun 22]. 1993–2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1217/.

[2] U. Lichter-Konecki, L. Caldovic, H. Morizono, K. Simpson, N. Ah Mew, E. MacLeod, Ornithine transcarbamylase deficiency, in: M.P. Adam, H.H. Ardinger, R.A. Pagon, S.E. Wallace (Eds.), GeneReviews® [Internet], University of Washington, Seattle, Seattle (WA), 2013 Aug 29 [Updated 2022 May 26]. 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154378/.

[3] V. Rüfenacht, J. Häberle, Mini-review: challenges in newborn screening for urea cycle disorders, Int. J. Neonatal Screen. 1 (2015) 27–35, https://doi.org/10.3390/ijns1010027.

[4] R.D. Kumar, L.C. Burrage, J. Bartos, S. Ali, E. Schmitt, S.C.S. Nagamani, C. LeMons, A deep intronic variant is a common cause of OTC deficiency in individuals with previously negative genetic testing, Mol. Genet. Metab. Rep. 26 (2021), https://doi.org/10.1016/j.ymgmr.2020.100706.

[5] Y.J. Jang, A.L. LaBella, T.P. Feeney, N. Braverman, M. Tuchman, H. Morizono, N. Ah Mew, L. Caldovic, Disease-causing mutations in the promoter and enhancer of the ornithine transcarbamylase gene, Hum. Mutat. 39 (2018) 527–536, https://doi.org/10.1002/humu.23394.

[6] S. Matsumoto, J. Häberle, J. Kido, H. Mitsubuchi, F. Endo, K. Nakamura, Urea cycle disorders—update, J. Hum. Genet. 64 (2019) 833–847, https://doi.org/10.1038/s10038-019-0614-4.

[7] L. Krivitzky, T. Babikian, H.S. Lee, N.H. Thomas, K.L. Burk-Paull, M.L. Batshaw, Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders, Pediatr. Res. 66 (2009) 96–101, https://doi.org/10.1203/PDR.0b013e3181a27a16.

[8] J. Häberle, A. Burlina, A. Chakrapani, M. Dixon, D. Karall, M. Lindner, H. Mandel, D. Martinelli, G. Pintos-Morell, R. Santer, A. Skouma, A. Servais, G. Tal, V. Rubio, M. Huemer, C. Dionisi-Vici, Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision, J. Inherit. Metab. Dis. 42 (2019) 1192–1230, https://doi.org/10.1002/jimd.12100.

[9] C.A. Thompson, Hidden on the X: Psychosocial Implications of Ornithine Transcarbamylase Deficiency in Female Carriers [master's Thesis], MA. Brandeis University, Waltham, 2016.

[10] M.L. Summar, N.A. Mew, Inborn errors of metabolism with hyperammonemia: urea cycle defects and related disorders, Pediatr. Clin. N. Am. 65 (2018) 231–246, https://doi.org/10.1016/j.pcl.2017.11.004.

[11] L.R. Soria, N. Ah Mew, N. Brunetti-Pierri, Progress and challenges in development of new therapies for urea cycle disorders, Hum. Mol. Genet. 28 (2019) R42–R48, https://doi.org/10.1093/hmg/ddz140.

[12] K.M. Stepien, T. Geberhiwot, C.J. Hendriksz, E.P. Treacy, Challenges in diagnosing and managing adult patients with urea cycle disorders, J. Inherit. Metab. Dis. 42 (2019) 1136–1146, https://doi.org/10.1002/jimd.12096.

[13] E. Murphy, Pregnancy in women with inherited metabolic disease, Obstet. Med. 8 (2015) 61–67, https://doi.org/10.1177/1753495X15576442.

[14] A.M. di Giulio, S. Carelli, R.E. Castoldi, A. Gorio, E. Taricco, I. Cetin, Plasma amino acid concentrations throughout normal pregnancy and early stages of intrauterine growth restricted pregnancy, J. Matern. Fetal Neonatal Med. 15 (2004) 356–362, https://doi.org/10.1080/14767050410001725578.

[15] K. Tihtonen, J. Uotila, J. Lähde, M. Salo, P. Keskinen, Risk of hyperammonemic coma in the puerperium: two cases of women with diagnosed and undiagnosed deficiency of urea cycle enzymes, Acta Obstet. Gynecol. Scand. 89 (2010) 404–406, https://doi.org/10.3109/00016340903540646.

[16] G. Wilcox, Impact of pregnancy on inborn errors of metabolism, Rev. Endocr. Metab. Disord. 19 (2018) 13–33, https://doi.org/10.1007/s11154-018-9455-2.

[17] H. Mendez-Figueroa, K. Lamance, V.R. Sutton, K. Aagaard-Tillery, I. van den Veyver, Management of ornithine transcarbamylase deficiency in pregnancy, Am. J. Perinatol. 27 (2010) 775–783, https://doi.org/10.1055/s-0030-1254240.

[18] S. Harris, N.L. Vora, Maternal genetic disorders in pregnancy, Obstet. Gynecol. Clin. N. Am. 45 (2018) 249–265, https://doi.org/10.1016/j.ogc.2018.01.010.

[19] S. Lamb, C.Y.L. Aye, E. Murphy, L. MacKillop, Multidisciplinary management of ornithine transcarbamylase (OTC) deficiency in pregnancy: essential to prevent hyperammonemic complications, BMJ Case Rep. 2013 (2013), bcr2012007416, https://doi.org/10.1136/bcr-2012-007416.

[20] G. Pinho, G. Ross, K. Krishnamoorthy, C. Kresge, L.Y. Shih, J.J. Apuzzio, S. F. Williams, Ornithine transcarbamylase deficiency and pregnancy: a case series and review of recommendations, Case Rep. Womens Health. 34 (2022), https://doi.org/10.1016/j.crwh.2022.e00390.

[21] K.L. Lindsay, C. Hellmuth, O. Uhl, C. Buss, P.D. Wadhwa, B. Koletzko, S. Entringer, Longitudinal metabolomic profiling of amino acids and lipids across healthy pregnancy, PLoS One 10 (2015), https://doi.org/10.1371/journal.pone.0145794.

[22] A. Hübler, J. Seidel, L. Patzer, K. Bellstedt, D. Schramm, Interdisciplinary treatment of early-onset ornithine transcarbamylase (OTC) deficiency-two patient reports and literature review, Z. Geburtshilfe Neonatol. 205 (2001) 236–241, https://doi.org/10.1055/s-2001-19056.

[23] B.A. McCullough, M. Yudkoff, M.L. Batshaw, J.M. Wilson, S.E. Raper, M. Tuchman, Genotype spectrum of ornithine transcarbamylase deficiency: correlation with the clinical and biochemical phenotype, Am. J. Med. Genet. 93 (2000) 313–319, https://doi.org/10.1002/1096-8628(20000814)93:4<313::AID-AJMG11>3.0.CO;2-M.

[24] M. Shimadzu, H. Matsumoto, T. Matsuura, K. Kobayashi, S. Komaki, K. Kiwaki, R. Hoshide, F. Endo, T. Saheki, I. Matsuda, Ten novel mutations of the ornithine transcarbamylase (OTC) gene in OTC deficiency, Hum. Mutat. S1 (1998) S5–S7, https://doi.org/10.1002/humu.1380110103.

[25] U. Ituk, O.C. Constantinescu, T.K. Allen, M.J. Small, A.S. Habib, Peripartum management of two parturients with ornithine transcarbamylase deficiency, Int. J. Obstet. Anesth. 21 (2012) 90–93, https://doi.org/10.1016/j.ijoa.2011.09.007.

[26] R. Sysák, K. Brennerová, R. Krlín, P. Štencl, I. Rusňák, M. Vargová, Effect of ornithine transcarbamylase (OTC) deficiency on pregnancy and puerperium, Diagnostics. 12 (2022), https://doi.org/10.3390/diagnostics12020415.

[27] D.R. Cordero, J. Baker, D. Dorinzi, R. Toffle, Ornithine transcarbamylase deficiency in pregnancy, J. Inherit. Metab. Dis. 28 (2005) 237–240, https://doi.org/10.1007/s10545-005-5514-4.

[28] M. Torkzaban, A. Haddad, J.K. Baxter, V. Berghella, W.A. Gahl, H.B. Al-Kouatly, Maternal ornithine transcarbamylase deficiency, a genetic condition associated with high maternal and neonatal mortality every clinician should know: a systematic review, Am. J. Med. Genet. A 179 (2019) 2091–2100, https://doi.org/10.1002/ajmg.a.61329.

[29] K. Gyato, J. Wray, Z.J. Huang, M. Yudkoff, M.L. Batshaw, Metabolic and neuropsychological phenotype in women heterozygous for ornithine transcarbamylase deficiency, Ann. Neurol. 55 (2004) 80–86, https://doi.org/10.1002/ana.10794.

[30] A. MacDonald, M. van Rijn, F. Feillet, A.M. Lund, L. Bernstein, A.M. Bosch, M. Gizewska, F.J. van Spronsen, Adherence issues in inherited metabolic disorders treated by low natural protein diets, Ann. Nutr. Metab. 61 (2012) 289–295, https://doi.org/10.1159/000342256.