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Two pregnancies of an ornithine carbamoyltransferase deficiency disease carrier and review of the literature

Dos embarazos de una portadora de la enfermedad por deficiencia de ornitina transcarbamilasa (OTC) y revisión de la literatura

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Abstract

Background: the underlying cause of the deficiency of ornithine carbamoyltransferase (OTCD) is a gene mutation on the X chromosome. In females, the phenotype is highly variable, ranging from asymptomatic to neurologic compromise secondary to hyperammonemia and it can be prompted by numerous triggers, including pregnancy.

Objective: the objective of this article is to report a case of two pregnancies of an OTCD-carrier, and to review the literature describing OTCD and pregnancy, parturition and postpartum.

Methods: an extensive search in PubMed in December 2021 was conducted using different search terms. After screening all abstracts, 23 papers that corresponded to our inclusion criteria were identified.

Results: the article focuses on the management of OTCD during pregnancy, parturition, and the postpartum period in terms of clinical presentation, ammonia levels and treatment.

Conclusions: females with OTCD can certainly plan a pregnancy, but they need a careful management during delivery and particularly during the immediate postpartum period. If possible, a multidisciplinary team of physicians, dietitians, obstetrician-gynecologist, neonatologists, pharmacists, etc. with expertise in this field should participate in the care of women with OTCD and their children during this period and in their adult life.

Keywords:

Hyperammonemia. OTC deficiency. Pregnancy. Parturition. Treatment..

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Resumen

Antecedentes: la causa subyacente de la deficiencia de ornitina transcarbamilasa (OTC) es una mutación genética en el cromosoma X. En las mujeres, el fenotipo es muy variable, desde asintomático hasta presentar un compromiso neurológico secundario a hiperamonemia, y puede ser provocado por numerosos factores desencadenantes, incluido el embarazo.

Objetivo: el objetivo de este artículo es reportar un caso de dos embarazos de una portadora de OTC, y revisar la literatura que describe OTC y embarazo, parto y posparto.

Métodos: se realizó una búsqueda exhaustiva en PubMed en diciembre de 2021 utilizando diferentes términos de búsqueda. Después de examinar todos los resúmenes, identificamos 23 artículos que correspondían a nuestros criterios de inclusión.

Resultados: el artículo se centra en el manejo de la OTC durante el embarazo, el parto y el posparto en términos de presentación clínica, niveles de amonio y tratamiento.

Conclusiones: las mujeres con OTC pueden planificar un embarazo, pero necesitan un manejo cuidadoso durante el parto, y particularmente, durante el posparto inmediato. Si es posible, un equipo multidisciplinar de médicos, dietistas, ginecólogos-obstetras, neonatólogos, farmacéuticos, etc., con experiencia en este campo, debe participar en el cuidado de las mujeres con OTC y sus hijos durante este periodo y en su vida adulta.

Palabras clave:

Hiperamonemia. Deficiencia de OTC. Embarazo. Parto. Tratamiento.

INTRODUCTION

The urea cycle is a set of six metabolic reactions whose main function is to eliminate the excess nitrogen that is formed in the degradation of amino acids and other nitrogen compounds. Of the six enzymes that catabolize these reactions, the deficiency of ornithine carbamoyltransferase (OTC) enzyme is the most common. The underlying cause of OTC deficiency (OTCD, OMIM number #311250) (1) is a gene mutation on the X chromosome, with a prevalence of one in 62,000-77,000 live births (2). Over 400 mutations have been found to result in OTCD. Of the identified disease-causing mutations reported for OTC, the majority are amino acid replacements, followed by RNA splicing defects, premature protein terminations and deletions (2). The mutation can occur *de novo* in the patient's genome or is inherited (3). Most of the patients with OTCD are hemizygous males. They can be severely affected, presenting with hyperammonemic coma, in the neonatal period, usually within the first week of life. Neonatal presentation generally correlates with the absence of liver OTC activity and null alleles (2). Partial enzyme activity usually translates to milder symptoms or later age of presentation. These symptoms can include nausea, vomiting, lethargy, confusion, ataxia, seizure, coma, and cerebral edema. The phenotype of carrier females is highly variable, ranging from asymptomatic to neurologic compromise secondary to hyperammonemia (4). Approximately 20 percent of female carriers become symptomatic (2). Reportedly, the degree of symptoms is related to the level of skewed X-inactivation within the liver (4). In females, the deficiency can appear during any period from infancy to adulthood and it can be prompted by triggers such as high protein intake, fasting, intercurrent illness, febrile illness, trauma, surgery, etc. Pregnancy, parturition, and the postpartum period can also be triggers since these situations can produce a major metabolic decompensation.

The diagnosis of OTCD is based on clinical suspicion in patients with elevated ammonia and liver function tests, considering the onset and the symptoms. Historically, the allopurinol test has been used to detect OTC carriers in at-risk females, however, its use is limited, since it has 91 % sensitivity (given by orotidine alone or in combination with orotic acid) and a specificity of 70 % and 65 %, respectively (5). Enzyme analysis and molecular genetic testing can identify OTCD as the underlying disease (3). Similar to other urea cycle disorders (UCDs), OTCD treatment includes a combination of a restriction/supplementation strategy. The restriction part comes from the dietetic treatment which is based on an individualized restriction of proteins (protein tolerance) and also depending on the clinical status. The latter is based on the supplementation with arginine or citrulline (6). Fasting periods longer than overnight time should be avoided.

Regarding the pharmacological treatment, this may include sodium benzoate and sodium or glycerol phenylbutyrate, which reduces ammonia by using alternative pathways for nitrogen elimination. Other modes of treatment include hemodialysis and liver transplantation. Lastly, similar to many metabolic diseases, OTCD is also a compelling candidate for gene therapy. Considering the overall treatment of these patients, it is recommended to avoid hepatotoxic drugs and also anticonvulsants (valproic acid), since they can induce episodes of decompensation (6,7).

Nowadays, UCDs (including OTCD) as well as other inborn errors of metabolism (IEM), represent a growing specialty in adult medicine. Reasons for this include improved diagnosis through expanded new-born screening programs, identification of potentially affected family members and greater awareness of symptomatic presentations in adolescence and in adulthood. Greatly improved survival and reduced mortality from previously lethal and debilitating conditions have enabled survival into adulthood and reproductive age (8).

When women with OTCD wish to become pregnant they will have to be referred to genetic counselling in order to understand the potential impact of pregnancy on their condition and vice versa and the outcome for their children. OTCD-carriers who become pregnant require a regular follow-up, a strict control of ammonia levels, diet or treatment when managing this critical period. There is scarce literature about the management of pregnancy in OTCD-carriers. In this article, a) we report a case of two pregnancies of an OTCD-carrier; and b) we review the literature describing OTCD and pregnancy, parturition and postpartum.

METHODS

The literature search was carried out in December 2021 and the strategy combined the following key terms: "urea cycle disorders, inborn", "ornithine carbamoyltransferase deficiency disease",

"ammonia", "hyperammonemia" with "pregnancy", "pregnancy outcome", "gravidity", "parity", "labor, obstretic", "parturition", "delivery, obstetric", "postpartum period" both as entry terms and MeSH terms in MEDLINE. There were no filters used and without time limit. We identified 1,049 papers. After screening all titles and abstracts, and eliminating duplicates, 23 papers that corresponded to our inclusion criteria were identified, which were: a) studies written in English, Spanish or French; b) performed in humans; and c) they reported data on women with OTCD during pregnancy, labor, or postpartum period. A thorough review of the references in the retrieved articles was also completed with citations from all searches imported into a reference manager (Mendeley). Informed consent of the patient has been obtained prior to data recollection and publication.

RESULTS

CASE REPORT

In this paper, we report the case of a 33-year-old woman who was sent to our Inherited Metabolic Diseases consult in 2013, in order to determine a possible metabolic disease due to hyperammonemia. Her delivery was normal (3,450 g) and had a normal psychomotor development. She underwent surgery for a liver adenoma in 2005 and has never had a problem with anesthesia. She had no family history of consanguinity or known metabolic diseases. She denied consumption of alcohol, drugs and/or smoking. She was not taking any medication at that time, had a university degree and worked as a teacher in a kindergarten.

The patient presented episodes of sleepiness as an infant that each time improved after fasting. At the age of three, she was treated due to an absence seizure, but she was not given a diagnosis. These episodes happened about two times a year, generally after a heavier meal, especially at noon. They lasted 24-48 hours until she got better. The episode repeated at the age of six and she was admitted again and treated with fluid therapy.

At the age of 17-18-years old, the patient was seen by neurologists. She was diagnosed with epilepsy and was given carbamazepine, but continued with absence seizures. Her crises consisted of drowsiness, decreased level of consciousness and forgetfulness. After trying to decrease the seizures with medications such as Depakine® and Keppra® without improving, she was switched to sodium valproate (Depakine chrono®). After six days taking it, she began with a decreased level of consciousness, behavioral changes, drowsiness, and was admitted to the hospital, where she remained for ten days. She had an ammonia of 300 mcg/dl (normal range, 19-80 mcg/dl). After the withdrawal of the medication and treatment with oral carnitine, she regained the level of consciousness. Three days after admission, she had an ammonia level of 140 mcg/dl (normal range 19-80 mcg/dl).

At diagnosis in our hospital, the patient presented an ammonia level of 74 µmol/l (normal range < 54 µmol/l) (Fig. 1). Plasma aminogram presented slight hypoaminoacidemia with a decrease in citrulline levels, 10 µmol/l (27 + 8) and Arg 12 µmol/l (72 + 26), and increased Gln levels 749 µmol/l (463 + 113). Urinary aminoacids: increased excretion of Gln 122 µmol/mol creatinine (58 + 25) and decreased Arg 1 µmol/mol creatinine (2 + 1). Elevated excretion of cystathionine 9 µmol/mol creatinine (2 + 2). Orotic acid in urine: 7.2 µmol/mol creatinine (0.1-2.9) and orotidine 1.4 µmol/mol creatinine (0.1-2.2). Urine organic acids: slightly increased excretion of homovanillic acid 37 µmol/mol creatinine (1-6) and orotic acid 10 µmol/mol creatinine (3-4). Normal levels of acylcarnitines. The study was completed with the allopurinol test, which was positive. Orotic acid in urine: basal, at 6 h, 12 h, 18 h and 24 h was 3.6 mmol/mol creatinine (normal range 0.1-2.9 mmol/mol creatinine), 24 mmol/mol creatinine, 17 mmol/mol creatinine, 51 mmol/mol creatinine and 5.4 mmol/mol creatinine, respectively.

The genetic test revealed a heterozygous mutation in exon 5 of the OTC gene, variant p.Ala135Pro (c.403G>C). The genetic study of her mother and three siblings showed no genetic mutation. The patient was prescribed citrulline supplementation, a low protein diet and medication for constipation.

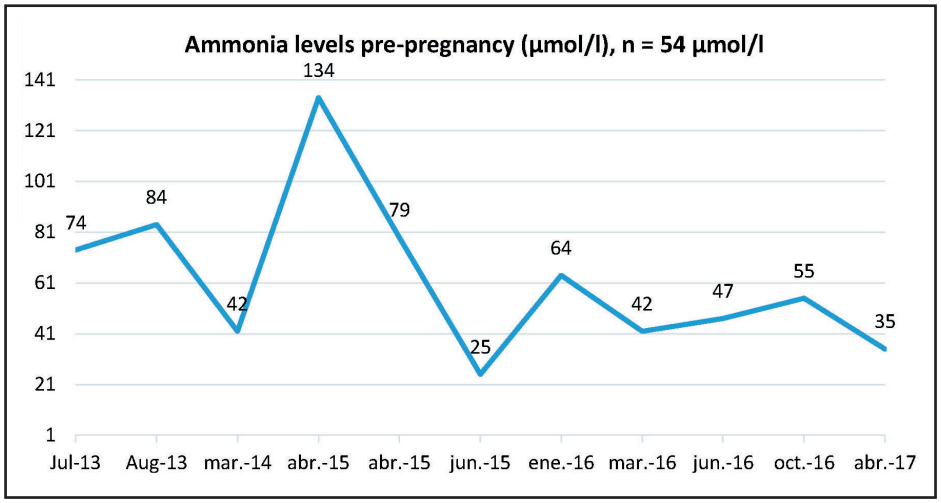

Figure 1.
Ammonia levels pre-pregnancy. .

The patient got pregnant spontaneously in October 2017. The ammonia levels of the patient pre-pregnancy and during pregnancy are shown in figures 1 and 2, respectively. The fact that in our case the fetus resulted in an unaffected female could have contributed to decreased levels of ammonia during pregnancy. The treatment of our patient was a combination of citrulline supplementation, reduced protein intake, ensured caloric intake and ensured hydration. We also developed a protocol of treatment that covered from the pre-pregnancy counselling to the postpartum and lactation (9,10) (Table I).

The patient delivered at 39.2 weeks by vacuum extraction. At delivery, the patient was asymptomatic and had normal levels of ammonia (Fig. 3). The treatment received during labor was intravenous 10 % glucose, ensured caloric intake, ensured hydration, citrulline supplementation and low protein diet. The fetus was an unaffected female who presented a weight of 3,300 g.

During postpartum, the patient was asymptomatic. On day 4 postpartum, she presented a maximum ammonia level of 122 µmol/l (normal range, < 54 µmol/l) (Fig. 3).

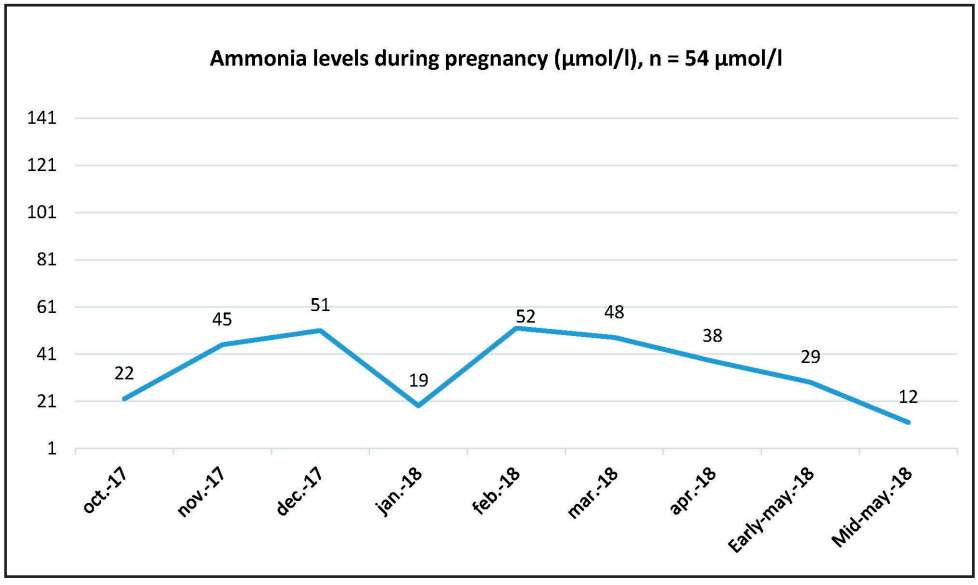

Figure 2.
Ammonia levels during pregnancy.

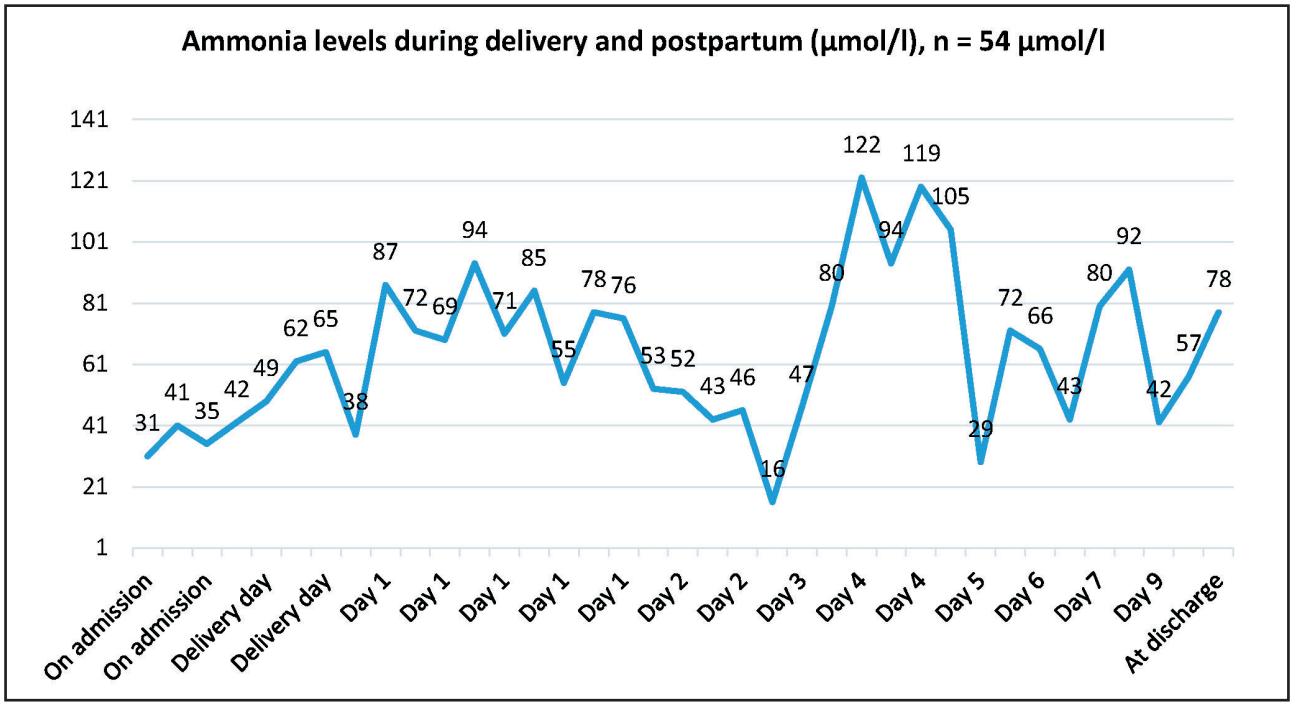

Figure 3.
Ammonia levels during delivery and postpartum.

Table I. Protocol for the management of pregnant women with OTCD

Pre-pregnancy	Ideally plan the pregnancy Genetic counselling
During pregnancy	Protein restricted diet Ensure caloric intake Avoid prolonged fasting Ensure hydration Arginine or citrulline supplements Monthly determinations of ammonia Quarterly determinations of plasma amino acids Hospitalization of decompensated patients Triggers: nausea, vomiting, constipation, prolonged fasting
Labor	Intravenous 10 % glucose Arginine or citrulline supplements Ensure hydration Ensure caloric intake (glucose and fat solutions, protein restriction) Avoid prolonged fasting Antiemetics (e.g., ondansetron) Early epidural anesthesia is recommended to reduce the catabolism and stress of delivery In case of anesthesia it is recommended to use reduced doses of midazolam, s-ketamine, phenanthyl, and isoflurane, in combination with infiltration of the surgical field with ropivacaine Avoid prolonged delivery Check food tolerance. Start oral diet as soon as possible Avoid hepatotoxic drugs during hospitalization Valproate and acetylsalicylic acid are contraindicated Corticosteroids can increase protein catabolism and should be avoided *Monitoring of ammonium levels:* Samples will be taken for urgent determination of ammonium levels (transported in ice) at admission in the delivery room and every 6 h during delivery If ammonia levels are higher than *54 µmol/l* in any determination, the ammonia levels will be monitored every 2 h until normalization If hyperammonemia *(54-150 µmol/l):* protein-free diet, intravenous 10 % glucoside (2,000 ml/day). Close monitoring of ammonia levels If hyperammonemia *(> 150 µmol/l):* ICU admission. Start specific treatment for hyperammonemia. Close monitoring of ammonia levels *Available medications:* – Glucose 10 % (rate of 3-4 mg/kg/min) ± insulin – Sodium phenylbutyrate, Amonal®, oral administration, dose of 5.5 g/m^2 (e.g., patient: height 173 cm and weight 68 kg, 10 g/day) – Sodium benzoate, reconstituted in 10 % glucoside, in a glass container and protected from light. Loading dose 5.5 g/m^2 (for a patient of 173 cm and 68 kg would be 10 g/day). Use the same amount for maintenance dose – Arginine: loading dose 200 mg/kg (e.g., patient: height 173 cm and weight 68 kg, 3 g/day). Use the same amount for maintenance dose. Do not mix in the same serum with the sodium benzoate If hyperammonemia *(> 250 µmol/l):* if significant encephalopathy and/or early high blood ammonia level or very early onset of disease (day 1 or 2). Close monitoring of ammonia levels. Begin hemo(dia)filtration if no rapid drop of ammonia within 3-6 hours If hyperammonemia above (> 500 µmol/l): start hemo(dia)filtration as fast as possible *Newborn monitoring:* Newborn monitoring is recommended in case the baby is affected and develops hyperammonemia

(Continues on next page)

Table I (cont.). Protocol for the management of pregnant women with OTCD

Postpartum	Intravenous 10 % glucose Arginine or citrulline supplements Ensure hydration Ensure caloric intake (glucose and fat solutions) Avoid prolonged fasting (> 6 h) Progressive use of dietary protein *Monitoring of ammonium levels:* Determination of ammonium levels every 4 h and then adjusted in each case for the risk of developing hyperammonemia If ammonia levels are higher than 54 µmol/l in any determination, the ammonia levels will be monitored every 2 h until normalization Use the same treatment methods as above
Hospitalization	A minimum hospitalization of 72 h for close monitoring is recommended
Breastfeeding	It is not contraindicated Ensure caloric intake Ensure hydration Avoid prolonged fasting Theoretically, lactation would be contraindicated if the newborn was affected and developed hyperammonemia. Use hypoproteic formula
Follow-up	Close follow-up in an outpatient metabolic clinic

OTCD: ornithine carbamoyltransferase deficiency; ICU: Intensive Care Unit.

The treatment of our patient was a combination of intravenous 10 % glucose, ensured caloric intake, ensured hydration, citrulline supplementation and low protein diet. However, during the episode of hyperammonemia (day 3-5 postpartum) she followed a protein free diet. She was discharged on day 18 postpartum. Our patient has also successfully breastfed her baby girl, with the exception of the days when hyperammonemia occurred. With the exception of citrulline supplementation, the patient was not prescribed any OTCD-specific medication during lactation. To ensure an adequate calorie intake, a maltodextrin module was prescribed.

In June 2019, the patient had a spontaneous abortion of a male fetus. A non-invasive prenatal testing (NIPT) was performed.

In December 2019, the patient got pregnant again. Invasive prenatal testing determined the fetus was a female. The ammonia levels of the patient pre-2nd pregnancy and during the 2nd pregnancy are shown in figures 4 and 5, respectively. The treatment included L-arginine and L-citrulline, L-carnitine, vitamin D supplementation, reduced protein intake, ensured caloric intake and ensured hydration, as well as medication for constipation. During this second pregnancy the same protocol we had developed previously was followed (Table I). The follow-up of this pregnancy happened during the COVID-19 pandemic (February-August 2020), which impacted the number of blood tests performed, and the telematic follow-up, to avoid unnecessary visits to the hospital.

The patient delivered at 39.1 weeks by spontaneous vaginal delivery. At delivery, the patient was asymptomatic and had normal levels of ammonia (Fig. 6). The treatment received during labor was intravenous 10 % glucose, ensured caloric intake, ensured hydra-

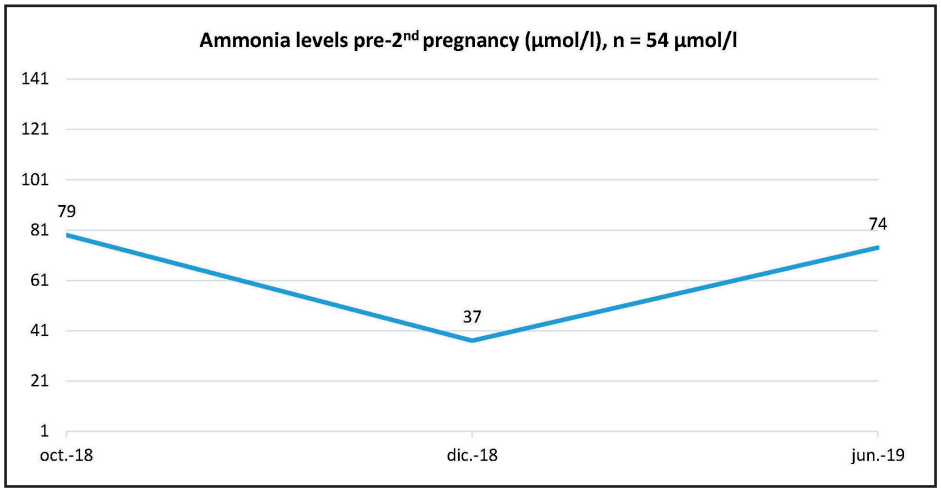

Figure 4.
Ammonia levels pre-2nd pregnancy.

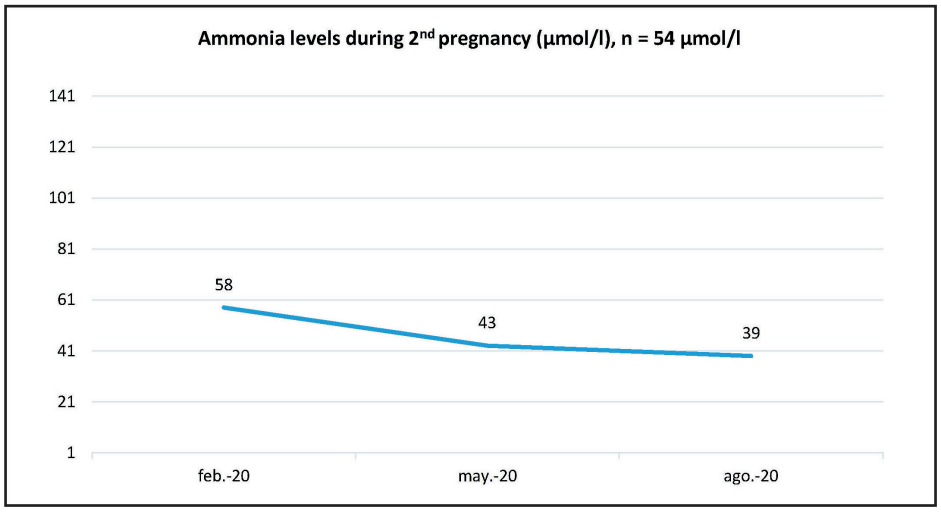

Figure 5.
Ammonia levels during 2nd pregnancy.

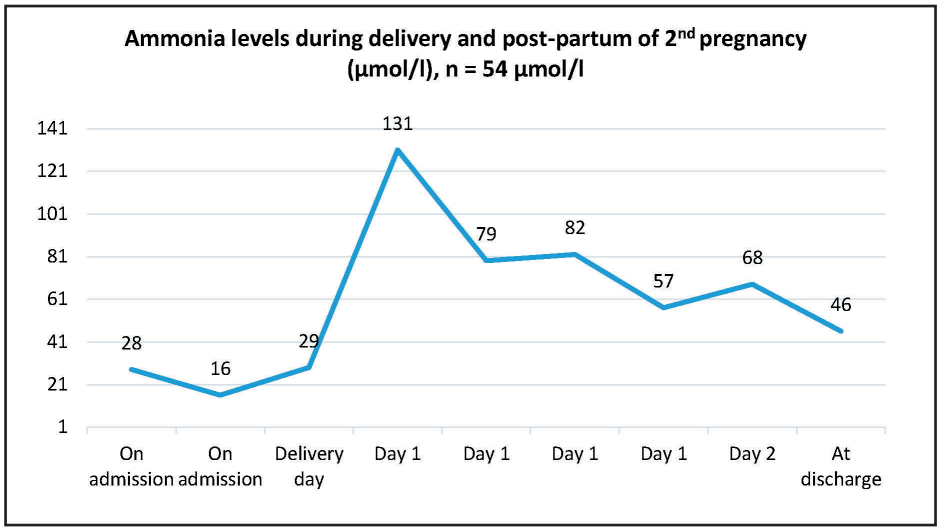

Figure 6.
Ammonia levels during delivery and postpartum of 2nd pregnancy.

tion, L-arginine and L-citrulline and low protein diet. The fetus was an affected female who presented a weight of 3,430 g. Genetic study showed the same mutation as the mother's.

During postpartum, the patient was asymptomatic. On day 1 postpartum, she presented a maximum ammonia level of 131 µmol/l (normal range, < 54 µmol/l) (Fig. 6). The treatment of our patient was a combination of intravenous 10 % glucose, ensured caloric intake, ensured hydration, L-arginine and L-citrulline supplementation and low protein diet. Our patient has also successfully breastfed her baby girl. Two months later, the patient had an ammonia level of 40 µmol/l (normal range, < 54 µmol/l). Both mother and daughters are well 4.9 years and 2.6 years later, respectively. The patient is actively followed-up in our outpatient clinic.

LITERATURE REVIEW

As a result of the literature review, 23 articles were retrieved regarding 33 cases of OTCD-carriers and pregnancy (Annex 1). The available evidence on OTCD in pregnancy comes mostly from case reports, small case series or literature reviews, and it dates from the past three decades, with the patients not being over 40-years of age. In these cases, the OTCD was either known prior to pregnancy (16 patients) or was diagnosed during pregnancy or shortly postpartum (18 patients). When the OTCD diagnosis was known, many reports described factors regarding pregnancy management such as the treatment provided, the ammonia levels and whether the mother was symptomatic or not throughout the whole process. During pregnancy, ten patients presented with hyperammonemia (11-19), seven patients with mental confusion (11,13,14,19-22), three patients with *hyperemesis gravidarum* (11,13,17) and one with acute liver failure (18). The risk of hyperammonemia was higher postpartum, especially between postpartum day 2 and day 11. During this period, 16 patients presented an increase in ammonia levels (9,12,15,20,21,23-31). In eight of the cases there was a fatal outcome, where the mother or the fetus died (11,21,28,31,32).

GENETIC MUTATION

Few studies described the mutations causing the disease, probably since many studies are historical and the possibility of studying it was low (11,15,17-19,32) (Annex 1). For those naming it, Weiss et al. mentioned their case as being a heterozygous c.919 A>G mutation in exon 9 of the OTC gene and also being a *de novo* mutation, since none of the parents had it (18). On the other side, Blair et al. found no pathogenic mutation. This occurs in approximately 30 % of biochemically confirmed OTCD cases and is likely due to intronic or promoter mutations. The genetic mutation of our patient (c.403G>C, p.Ala135Pro) has never been reported. Caldovic et al. have recently published the fifth mutation update for human OTC. After examination of publicly available genomic data and examination of phenotype/genotype correlations from patients participating in the Urea Cycle Disorders Consortium Longitudinal Study, they reported 417 disease-causing mutations in the OTC gene, fifty-two patients with OTCD due to deletions, duplications or complex rearrangements involving the OTC gene and also 44 rare sequence variants in the OTC gene (2). Additionally, the authors found no correlation between the type of mutation and severity of disease measured by either number of hyperammonemic episodes or liver dysfunction in patients with late onset OTCD.

PREGNANCY DESCRIPTION

Clinical presentation

Similar to our patient, some of the included studies described no symptoms of OTCD during pregnancy, while others reported a manifestation of the disease as early as seven weeks into pregnancy (18). The adverse pregnancy outcomes reported have been mainly neurological, psychiatric, or hepatic (19) (Annex 1). In the study by Weiss et al., at seven weeks pregnant, the patient affected by *hyperemesis gravidarum* (intractable vomiting, weight loss and mildly elevated transaminases) developed acute liver failure and coma (18). In pregnancy, UCDs must be included in the differential diagnosis of *hyperemesis gravidarum* or acute liver failure, which must prompt plasma ammonia determination. A careful medical and family history is mandatory and should include questions about unexplained neonatal deaths, neurological or psychiatric disorders in the family, evidence of protein avoidance in patient and family members and drug intake by the patient (6). Pregnancy-related issues (nausea, vomiting, and anorexia) can lead to acute metabolic decompensation due to reduced calorie intake and difficulties taking essential supplements and medications. Although rare, if prompt treatment is not given, such decompensation can be sufficiently severe so as to lead to maternal and/or fetal death (11,15,33).

Ammonia levels

Since in many cases the OTCD was unknown until postpartum (in some cases postmortem), many patients did not have determinations of ammonia levels during pregnancy (15,20-22). The lack of ammonia levels determinations combined with an ostensibly healthy patient conducted in many cases for the OTCD to go unnoticed during the pregnancy period. On top of that, given the increased nitrogen demands during this time, the pregnancy period was unremarkable for some patients. On the other side, several studies reported hyperammonemia during pregnancy (12-19). The potential deleterious consequences of hyperammonemia on the fetus at an early term of pregnancy are uncertain. Compared to other metabolic diseases, in OTCD, data regarding the possible fetal toxicity of high levels of ammonia is not completely known (18). For instance, in phenylketonuria, high maternal phenylalanine levels are teratogenic to a developing fetus *in utero* (33). Ammonia levels should be checked regularly during pregnancy in patients with OTCD. Our patient presented normal levels of ammonia during pregnancy, something confirmed in some of the published cases (9,26).

Treatment

Pregnant women with OTCD should maintain the prescribed dietary treatment, according to the individual protein tolerance, and aminoacids supplements. Plasma amino acids should be checked regularly during pregnancy. The increased energy and protein requirements during pregnancy should be considered to avoid endogenous catabolism. Fasting periods longer than overnight time should be avoided. There are few reports on the use of specific medications (sodium benzoate and sodium phenylbutyrate), to control the ammonia levels during pregnancy (11-16,18,19,21). None of the articles described any teratogenic effects of the drugs and neither manufacturers' data do not provide substantial information on their use in pregnancy. Annex 1 describes the outcomes of these cases. Additional treatment used to lower the ammonia levels included hemodiafiltration (13,17), hemofiltration (19) and hemodialysis (18) described in four of the clinical reports.

DELIVERY DESCRIPTION

Timing and mode of delivery

Regarding the timing and/or the mode of delivery, some of the studies did not contain this data, however the information extracted reports pregnancies going from 31 weeks (the lowest reported) up to term, whereas the mode of delivery varied between a cesarean section, a spontaneous vaginal delivery or an induction of labor. There are no specific recommendations on the mode of deliver for OTCD patients. In the absence of other complications, vaginal delivery is usually possible (33). According to Méndez-Figueroa et al., an induction of labor at 39 weeks should be considered, to ensure the presence of all services and medical specialties for management (9).

Labor description

From a metabolic standpoint, parturition represents prolonged and intense muscular activity where the energy requirements are substantial (8), and women often have poor oral intake for the duration of labor (33). Once admitted to labor and delivery, patients can be classified as low risk or high risk to guide the most appropriate management. A patient is high risk if she has had previous episodes of hyperamonemic coma, recurrent episodes of hyperammonemia as an adult or metabolic decompensation during this or prior pregnancies (9). Depending on the low/high risk patient, an adequate peripheral or central intravenous access should be secured. Euglycemia should be maintained throughout the period of delivery. Blood glucose monitoring should be carried-out every 2-4 h (9,25,26,32,33). The aim is to keep blood sugars 60-100 mg/dl at all times. Hemodynamic stress can be reduced by appropriate analgesia and decreasing patients' anxiety. Liaison with the obstetrician, obstetric anesthetist and neonatology prior to delivery is advised. Considering these issues, these deliveries should be performed in a hospital setting. Our patient did not present any symptoms of OTCD during labor, similar to many cases described in the literature.

Ammonia levels

Only a few patients had ammonia levels determinations during labor (9). Méndez-Figueroa et al. recommend that, during labor, ammonia levels should be determined upon admission and every six hours (9). However, these determinations should be more frequent if the patient is symptomatic, or the values are above normal (Table I). Our patient presented normal levels of ammonia during labor.

Treatment

According to the literature, the treatment used in these patients during labor was mainly intravenous lactated Ringer's solution, intravenous 10 % glucose and L-citrulline. The idea behind the treatment was to avoid catabolism during this critical period (Table I). In the case of our patient, a combination of intravenous 10 % glucose, ensured caloric intake, ensured hydration, L-citrulline, low protein diet was used. A scheduled cesarean section preceded by overnight fasting could theoretically precipitate hyperammonemia, therefore intravenous hydration using 10 % dextrose is recommended (9). If epidural anesthesia is used, additional hydration with lactated Ringer's solution as needed may be used (9,25,26,32,33). However, this solution must be cautiously used, since it can be dangerous in other pathologies that cause increased ammonium, when the disease has not yet been confirmed (34). The patient's usual treatment with arginine or citrulline should be maintained during this time. Since some of the medications used to treat OTCD patients are not readily available, the hospital pharmacy should be involved early with management plans (9).

POSTPARTUM DESCRIPTION

Clinical presentation

Following delivery of the fetus and placenta, maternal endocrine and metabolic status changes abruptly (8). Postpartum metabolic decompensation is frequent in OTCD, as well as other metabolic disorders. Elevations in postpartum metabolites have also been described in other disorders of protein metabolism such as maple syrup urine disease and methylmalonic acidemia (33). In symptomatic patients, the symptoms appeared between postpartum days 2 to 11. Some of the symptoms included nausea, vomiting, diplopia, ataxia, progressive somnolence (31), and even severe cerebral edema (31) and coma (23). In our review, three of the patients died as a result of OTCD complications (31). In the study by Açikalin et al. the patient was hospitalized on the second postpartum day because of nausea and vomiting, altered mental status, disorientation, and seizure activities. She was diagnosed as postpartum coma due to hyperammonemia related to OTCD and after 14 days of hospitalization, she died in the ICU despite all of the supportive and specific treatment modalities (28). Our patient did not present any symptoms of OTCD postpartum, similar to many cases described in the literature.

Ammonia levels

The exact cause of postpartum hyperammonemia is not well understood. It is hypothesized that when there is an unaffected fetus, the liver detoxifies maternal ammonium and, when this relationship is disrupted at the time of delivery, maternal ammonium increases (24). Following delivery of the fetus and placenta, the uterus undergoes involution (the process in which the uterus decreases in size, following delivery) producing increased protein catabolism. Uterine involution is especially rapid in the first 10-14 days' postpartum; by six weeks' postpartum it has returned to pre-pregnancy size. This is therefore a period of exceptionally high risk for decompensation of OTCD in at risk mothers, with many OTCD presenting for the first time in the postpartum period (8). Our patient presented moderate hyperamonemia up to 122 µmol/l (normal range, < 54 µmol/l) and 131 µmol/l (normal range, < 54 µmol/l) during the first and second pregnancy, respectively. In both cases, that responded to dietary modification without the use of any specific drug.

Treatment

In case of postpartum hyperammonemia, the treatment of choice was a low-protein diet (9,12,15,20,23,25,27,30), ammonia scavengers (sodium benzoate and sodium phenylbutyrate) (9,12,15,20,21,23-28,30,31), and hemodialysis/hemofiltration (20,28,30,31).

Discharge day

According to the literature, the most dangerous period for developing hyperammonemia and other OTCD symptoms is postpartum, therefore, this will have to be considered when discharging an OTCD carrier.

Breastfeeding

Only two of the studies reported women who successfully breastfed their baby girls. One of the newborns had OTCD. Both mothers were taking specific medications used to stimulate nitrogen excretion (sodium benzoate and sodium phenylbutyrate) when lactation started. Breastfeeding is a topic that needs to be discussed on an individual basis between women wishing to breastfeed and their physicians. Since breastfeeding places extra energy demands on the mother, with energy and nutrients being diverted to milk production from the third postpartum day (e.g., the uterine involution mobilizes amino acids for lactation), it is important to ensure an adequate calorie intake (8,33). During lactation, the composition of human milk changes dynamically and may vary according to many maternal factors, such as the nutritional status. Maternal undernutrition, producing lack of vitamin B12, vitamin D, calcium, and DHA during lactation may lead to low vitamin content in breast milk, which can cause permanent neurological disabilities in infants or low bone mineralization (35). On top of that, the combination of the catabolic state of the puerperium with the nutritional demands of breastfeeding and a poor calorie intake may be a potential trigger for metabolic decompensation. Moreover, since pregnancy, labor and puerperium can be associated with citrulline or arginine deficiencies, which can increase ammonia build-up, their prescription will have to be ensured, especially if the patient is breastfeeding (9). Currently, there is very little safety information available regarding many of the specific medications used or their content in breast milk (26,33,36). On the other side, there is a need to consider the clinical status of the newborn, whether it is affected by the disease or not, and follow the nutritional guidelines recommended in each case. Overall, both mother and child should be closely monitored during lactation.

FOLLOW-UP AND OVERALL OUTCOME

Women should be monitored in the hospital for at least 72 hours after delivery, and close follow-up in an outpatient metabolic clinic should be recommended.

Limitations

There is scarce literature about the management of pregnancy in OTC carriers and the information available comes from non-analytic studies: single case reports, small case series or literature reviews.

Annex 1. Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
			Genetic mutation	– Maternal description: symptomatic/asymptomatic – Ammonia levels (normal levels, NL) – Treatment	*Mode of delivery* (SVD/CS/IOL/VE)	– Maternal description: symptomatic/asymptomatic – Ammonia levels (normal levels, NL) – Treatment – Fetal description: normal/affected, sex (male/female), weight at birth (g)	– Maternal description: symptomatic/asymptomatic – Ammonia levels (normal levels, NL) – Treatment – Discharge day – Breastfeeding: yes/no – Follow-up
Arn et al., 1990	Case reports	21	Unknown N/A	– Asymptomatic – N/A – N/A	– 38 – N/A	– Asymptomatic – N/A – N/A – N/A, male, 2,760 g	– Symptomatic postpartum day 8: headache, confusion, uncommunicative. Severe cerebral edema. The patient died – 226 µmol/l to 411 µmol/l (normal range, < 40 µmol/l) – Lactulose, intravenous sodium benzoate, intravenous arginine hydrochloride, hemodialysis, intravenous sodium phenylacetate

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Annex 1. Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Arn et al., 1990	Case reports	22	Known N/A	– Asymptomatic – N/A – N/A	– N/A – N/A	– Asymptomatic – N/A – N/A – N/A, Female, 3,810 g	– Symptomatic postpartum day 3: nausea, vomiting, diplopia, ataxia, progressive somnolence – 161 µmol/l to 211 µmol/l (normal range, < 40 µmol/l) – Lactulose, intravenous sodium benzoate, intravenous sodium phenylacetate – N/A – N/A – N/A
Arn et al., 1990	Case reports	32	Unknown Retrospectively identified as a carrier of a mutant OTC allele (pedigree analysis)	– N/A – N/A – N/A	– N/A – N/A	– N/A – N/A – N/A – N/A, N/A, N/A	– Symptomatic postpartum day 8: status epilepticus. The patient died – N/A – N/A
Schimanski et al., 1996	Case report	24	Unknown Deletion of two nucleotides (T892, G893) in exon 9	– Symptomatic at 14 weeks: weight loss, sudden episodes of mental confusion, hyperemesis gravidarum. Hyperammonemia following treatment with TPN including amino acids and vitamin K – 23.5 µmol/l - 380 µmol/l (normal range, N/A) – Benzoate *Pregnancy was terminated* *The patient developed signs of cerebral edema and died*			
Redonnet-Vernhet et al., 2000	Case report	27	Known N/A	– Asymptomatic (despite persistent hyperammonemia, no neurologic impairment) – 104 µmol/l (normal range, N/A) – Low-protein diet, L-arginine, sodium phenylbutyrate	– 33 – SVD	– Asymptomatic – N/A – N/A – Unaffected, female, 2,080 g	– Asymptomatic – 116-426 µmol/l (normal range, N/A) – Low-protein diet, sodium phenylbutyrate, l-arginine – N/A – N/A – Four months later, plasma ammonia of the patient was normal. The infant developed with normal ammonia

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Peterson, 2003	Case report	28	Unknown N/A	– Symptomatic at 31 weeks: complaints of regular uterine contractions, fatigue, and dysuria – N/A – Treated for pyelonephritis and preterm labor	– 31 – CS	– Asymptomatic – N/A – N/A – Affected, male, 2,339 g	– Symptomatic postpartum day 3: acute mental status (periodic episodes of nausea, emesis, headache, confusion, lethargy, decorticate decerebrate posturing, delirium, coma) – 180 µmol/l (day 3) (normal range, 11-35 µmol/l) – Oral lactulose, sodium benzoate, sodium phenylacetate, low-protein diet – Day 8 – N/A – N/A
Cordero et al., 2005	Case report	24	Known Presumed heterozygous for OTCD	– N/A – 52 µmol/l (normal range, N/A) – Low-protein diet	– At term – IOL	– Asymptomatic – 62 µmol/l (normal range, N/A) – Intravenous 10 % glucose, sodium benzoate – Unaffected, male, N/A	– Asymptomatic – 137 µmol/l (day 3) (normal range, N/A) – Sodium benzoate – Day 6 (uncertain) – N/A – N/A
Crosbie et al., 2009	Case report	39	Unknown N/A	– Symptomatic at 12 weeks: confusion and fluctuating level of consciousness. Daily hyperemesis over the previous 3 weeks – 288 µmol/l (normal range, 11-35 µmol/l) – Sodium benzoate, hemodiafiltration, intravenous arginine, parenteral dextrose, intralipid, enteral feeding. On day 7 oral feeding was introduced, oral sodium benzoate and citrulline (replacing arginine) *The patient was discharged on day 21 on a low-protein diet and follow-up arrangements*	– N/A – N/A	– N/A – N/A – Unaffected, N/A, N/A	– N/A – N/A – N/A – N/A – N/A – N/A

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Méndez-Figueroa et al., 2010	Case reports Review	23	Known Heterozygous c.122A>G (p.D41G) mutation in exon 2 of the OTC gene	– Asymptomatic – N/A – Self-restricted protein diet	– 37 – IOL	– Asymptomatic – N/A – Intravenous 10 % dextrose, insulin, oral L-citrulline – Affected, male, 2,775 g	– Asymptomatic – 35 µmol/l (normal range, < 25 µmol/l) – Protein-restricted diet, oral sodium benzoate – Day 3 – N/A – N/A
Méndez-Figueroa et al., 2010	Case reports Review	28	Known Heterozygous OTCD (pedigree analysis)	– Asymptomatic – N/A – N/A	– 35 – SVD	– Asymptomatic – 98 µmol/l (normal range, < 25 µmol/l) – Oral sodium benzoate – N/A, female, 2,412 g	– Asymptomatic – Normal levels – Protein-restricted diet, oral citrulline – Day 5 (uncertain) – N/A – Serum ammonia remained normal 4 months later
Méndez-Figueroa et al., 2010	Case reports Review	32	Known N/A	– Asymptomatic – Normal levels – Protein-restricted diet, oral citrulline	– 38 – CS	– Asymptomatic – N/A – Intravenous lactated Ringer's solution – Unaffected, male, 3,440 g	– Asymptomatic – N/A – Protein-restricted diet, oral citrulline – Day 5 – N/A – Serum ammonia levels were normal 3 months later
Méndez-Figueroa et al., 2010	Case reports Review	16	Unknown c.122A>G (p.D41G) mutation on exon 2 of OTC gene	– N/A – N/A – N/A	– 38 – SVD	– Asymptomatic – N/A – Intravenous lactated Ringer's solution – N/A, male, 3,680 g	– Asymptomatic – N/A – N/A – Day 2 – N/A – At postpartum day 3, following a hypoxic episode of the baby, both the mother and the infant were diagnosed with OTCD

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Méndez-Figueroa et al., 2010	Case reports Review	18	Unknown c.904C>T (p.H302Y) in exon 9 of the OTC gene	– Asymptomatic (except for nausea and vomiting early in pregnancy) – N/A – N/A	– 36w+6d – Forceps assisted vaginal delivery	– Asymptomatic – N/A – Intravenous lactated Ringer's solution – N/A, male, 3,265 g	– Asymptomatic – N/A – N/A – Day 2 – N/A – Postpartum day 8, following an inadequate feeding and lethargy of the infant, both the mother and the infant were diagnosed with OTCD
Méndez-Figueroa et al., 2010	Case reports Review	31	Known Mutation in exon 5 of the OTC gene	– Asymptomatic – N/A – N/A	– 39.4 days – SVD	– Asymptomatic – N/A – Intravenous D10W – Affected, male, 3,745 g	– Asymptomatic – N/A – Regular diet – Day 2 – N/A – Follow-up normal visits
Tihtonen et al., 2010	Case report	23	Known N/A	– Asymptomatic – N/A – N/A	– 37 – CS	– Asymptomatic – N/A – Intravenous 10 % glucose, sodium benzoate, L-arginine – Affected, female, 2,830 g	– Asymptomatic – 79 µmol/l (normal range, < 50 µmol/l) – Intravenous 10 % glucose, sodium benzoate, L-arginine, low protein diet, peroral sodium phenylbutyrate – Day 7 – Yes – The newborn was followed-up in the neonatal unit and started citrulline treatment. Ammonia levels remained within the normal range

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Quintero-Rivera et al., 2010	Case reports	32	Unknown 119 kb deletion on Xp11.4 including the OTC gene	– Symptomatic: pregnancy-induced hypertension – N/A – Self-chosen vegetarian diet	– At term – CS	– Symptomatic: severe intrapartum complications – N/A – N/A – Affected, male, N/A *The fetus died. The clinician and pathologist assigned the cause of death to hypoxic-ischemic encephalopathy*	– N/A – N/A – N/A – N/A – N/A – N/A
Quintero-Rivera et al., 2010	Case reports	33,5	Unknown 119 kb deletion on Xp11.4 including the OTC gene	– Symptomatic: pregnancy-induced hypertension – N/A – Self-chosen vegetarian diet	– 32 – CS	– N/A – N/A – N/A – Affected, male, 1,615 g – The fetus died	– N/A – N/A – N/A – N/A – N/A – N/A
Celik et al., 2011	Case report	31	Unknown No pathogenic mutation, however, heterozygous for 3 polymorphisms (K46R, Ivs3-8A4T, Q27OR) exons 2, 4, 8	– Symptomatic: mental confusion – 179 µg/dl (normal range, 19-60 µg/dl) – Oral sodium phenylbutyrate, oral arginine, ornithine and lysine, protein-restricted diet	– N/A – SVD	– Asymptomatic – Normal range – N/A – Unaffected, male, N/A	– Asymptomatic – Normal range – N/A – Day 5 – N/A – Follow-up normal visits

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Lipskind et al., 2011	Case report	26	Known N/A	– Symptomatic at 33 weeks: fever, nausea, vomiting, contractions, mental status progressively deteriorated – N/A – Treated for preterm labor	– 33 – SVD	– Symptomatic – N/A – N/A – Unaffected, male, 2,240 g	– Symptomatic postpartum: unresponsive, agonal breathing, coma – 231 µmol l^{-1} (normal range, 7-35 µmol l^{-1}) – Intravenous dextrose, lactulose, intravenous sodium benzoate, hemofiltration, protein-free TPN. Later on, oral sodium phenylbutyrate, protein-restricted diet – Day 18 – N/A – The patient was mentally and neurologically intact and her ammonia levels remained normal 6 weeks later
Langendonk et al., 2012	Case reports	24	Known R141Q mutation in the OTC gene	– Symptomatic during first trimester: periods of hyperammonemia, nausea and drowsiness – 117-129 µmol/l (normal range, < 40 µmol/l) – Low-protein diet, amino acid supplementation, sodium benzoate, citrulline, calcium, folic acid, vitamin B6, LMW heparin	– 37 – SVD	– Asymptomatic – 60 µmol/l (normal range, < 40 µmol/l) – No specific treatment – Unaffected, female, 2,830 g	– Symptomatic postpartum day 11: associated agitation – 130 µmol/l (day 3) and 279 µmol/l (day 11) (normal range, < 40 µmol/l) – Maintained caloric intake, sodium benzoate, citrulline, amino acid supplementation, restricted protein diet, sodium phenylbutyrate – Day 19 – Yes – Both mother and daughter were well 12 years later
Langendonk et al., 2012	Case reports	27	Known R141Q mutation in the OTC gene	– N/A – N/A – Low-protein diet, amino acid supplementation, sodium benzoate, citrulline, calcium, folic acid, vitamin B6, LMW heparin *Affected male fetus. Termination*			

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Ituk et al., 2012	Case reports	43	Known N/A	– Symptomatic at 12 weeks pregnant: confusion and altered mental status – N/A – Calcium supplementation, restricted protein diet, 10 % dextrose, arginine, citrulline	– 37 – IOL	– Asymptomatic – Normal levels – Intravenous 10 % dextrose, 0.45 % saline, lactated Ringer's solution, intravenous phenylephrine, ondansetron – Unaffected, female, 2,630 g	– Asymptomatic – 72 µmol/l (day 3) (normal range, 16-50 µmol/l) – N/A – Day 3 – N/A – N/A
Ituk et al., 2012	Case reports	33	Known N/A	– Asymptomatic – N/A – Controlled protein intake, carnitine, citrulline, sodium phenylacetate	– 38 – IOL	– Asymptomatic – 91 µmol/l (normal range, N/A) – Sodium benzoate, sodium phenylacetate, 10 % arginine, 10 % dextrose and intralipid – Affected, male, 2,980 g *The fetus died 10 days later from OTCD complications*	– Symptomatic postpartum day 7: altered level of consciousness – 155 µmol/l (normal range, N/A) – Intravenous arginine, sodium phenylacetate, sodium benzoate – Discharge day 2 (first hospitalization) and day 9 (second hospitalization) – N/A – N/A
Lamb et al., 2013	Case report	29	Known N/A	– Asymptomatic – Normal level – Sodium benzoate, sodium phenylbutyrate, restricted protein diet, arginine, essential amino acid, multivitamin and ω3 supplements	– 40 + 4 – IOL	– Asymptomatic – Normal levels – Intravenous 10 % dextrose, oral glucose polymer, antiemetic, patient´s regular medication – Unaffected, male, 3,050 g	– Asymptomatic – 91 µmol/l (normal range, < 35 µmol/l) – Oral glucose polymer, sodium benzoate – Day 8 – No Both mother and baby were well 6 weeks later

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Blair et al., 2014	Case report	38	Unknown No pathogenic mutation	– N/A – N/A – N/A	– N/A – CS	– N/A – N/A – N/A – N/A, N/A, N/A	– Symptomatic postpartum day 5: acute onset behavioral disturbance – 292 µmol/l (normal range, 10-50 µmol/l) – Sodium benzoate, arginine, reduced protein diet, intravenous 10 % dextrose, 20 % lipid emulsion – N/A – N/A – She remained well 12 months later
Kersale et al., 2014	Case report Letter	32	Unknown N/A	– N/A – 173 µmol/l (normal range, 11.2-35.4 µmol/l) – Sodium benzoate, sodium phenylacetate, L-carnitine, citrulline, parenteral nutrition (initially only glucose and lipids) followed by enteral nutrition	– N/A – N/A	– N/A – N/A – N/A – Affected, female, N/A	– N/A – N/A – N/A – N/A – Day 120 – N/A – N/A
Nakajima et al., 2014	Case report	28	Unknown Heterozygote mutation exon 8 R277W (829 C>T)	– Symptomatic at 16 weeks: hyperemesis gravidarum – 268 µg/dl (normal range, N/A) – Glucose, lactulose, kanamycin sulfate, hemodiafiltration *The patient was hospitalized for 56 days. Pregnancy was terminated*			
Bailly et al., 2015	Case report	32	Unknown Novel heterozygous mutation p.Ala209Glu (c.626C>A) in the OTC gene	– Symptomatic at 20 weeks: progressive neuropsychological disorders associated with behavior disorders. Impaired consciousness and coma – 173 µmol/l (normal range, N/A) – Sodium benzoate, citrulline, sodium phenylacetate, hemofiltration, and reduced protein intake	– N/A – N/A	– N/A – N/A – N/A – Affected, female, N/A	– N/A – N/A – N/A – N/A – N/A – N/A – Symptomatic: mild cognitive impairment 3 months later. The baby girl had no sequelae at 11 months

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Açikalin et al., 2016	Case report	24	Unknown N/A	– N/A – N/A – N/A	– N/A – SVD	– N/A – N/A – Unaffected, N/A, N/A	– Symptomatic postpartum day 2: nausea, vomiting, altered mental status, disorientation, seizures, and coma. The patient died – 452 µmol/l (normal range, N/A) – Sodium benzoate, hemodialysis
Weiss et al., 2017	Review	28	Unknown Heterozygous c.919 A>G mutation in exon 9 of the OTC gene	– Symptomatic at 7 weeks pregnant: acute liver injury, acute liver failure, coma – 281 µmol/l (normal range, < 50 µmol/l) – Protein-free diet, hemodialysis, sodium benzoate, arginine, citrulline supplements	– 39 – IOL	– Asymptomatic – N/A – Intravenous carbohydrates and lipids – Unaffected, female, N/A	– N/A – N/A – Intravenous carbohydrates and lipids – N/A – N/A – Asymptomatic 3 years later
Kido et al., 2017	Case report	37	Known Diagnosis: liver biopsy	– N/A – N/A – Self-restricted protein diet, L-carnitine	– 41w+1d – VE	– Asymptomatic – 68 µmol/l at delivery, 59 µmol/l at 10 h and 54 µmol/l at 24 h after delivery (normal range, N/A) – N/A – N/A	– Symptomatic: postpartum day 4: hyperammonemia – 194 µmol/l (normal range, N/A) – Arginine, citrulline – Discharge day 6. The patient was hospitalized upon discharge with impaired consciousness, after excessive protein intake. Ammonia levels: 180 µmol/l (normal range, N/A). She received intensive treatment for hyperammonemia – N/A – At the time of publication, the patient was using medication and had been able to raise her child following hospital discharge

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Annex 1 (cont.). Review of reported cases of OTCD in pregnancy

Author(s), year	Publication type	Age (years)	OTCD diagnosis (known/unknown)	Pregnancy description	Timing (weeks)	Labor description	Postpartum description
Algahtani et al., 2018	Case report	26	Unknown Heterozygous c.626C>T (p.Ala-209Val)	– N/A – N/A – N/A	– N/A – N/A	– N/A – N/A – N/A – N/A	– Symptomatic: at postpartum day 7 she presented with a 2-day history of dizziness, diminished level of consciousness, vomiting and seizures. She had been diagnosed with multiple sclerosis and depression 4 years earlier – 274 µmol/l (normal range, 10.71-32.13 µmol/l) – Steroid therapy (intravenous and oral). After OTCD diagnosis, she was treated with hemodialysis, sodium benzoate, arginine, protein-restricted (nasogastric feeding) – N/A – N/A – Asymptomatic 5 years later
Lefrère et al., 2019	Case report	22	Unknown N/A	– Symptomatic at 9 weeks pregnant: uncontrollable cyclical vomiting that required multiple hospitalizations. At 26 weeks pregnant: hematemesis, esophagitis and gastritis, and deterioration of general status. Episode of acute psychomotor agitation. Undernutrition – N/A – Unspecific undernutrition treatment (until OTCD diagnosis). Afterwards, intravenous glucose 10 %, intralipid 20 %	– 32 – N/A	– N/A – N/A – N/A – Unaffected, male, 1,400 g	– N/A – N/A – N/A – Day 30 – N/A – N/A

OTCD: omithine transcarbamylase deficiency; SVD: spontaneous vaginal delivery; CS: cesarean section; IOL: induction of labor; VE: vacuum extraction; N/A: not available.

For this reason, it is highly important to develop protocols/clinical guidelines that will guide the physicians in managing this condition during pregnancy. Nevertheless, our work provides relevant information regarding pregnancy managing in OTCD and highlights the importance of protocols ready to follow during pregnancy, labor and postpartum.

CONCLUSIONS

Females with OTCD can certainly plan a pregnancy, but they need a careful management during delivery and particularly during the immediate postpartum period. If possible, a multidisciplinary team of physicians, dietitians, obstetricians-gynecologists, neonatologists, pharmacists, etc. with expertise in this field, should participate in the care of women with OTCD during pregnancy and in their adult life. Increased awareness of these conditions amongst all clinicians is essential to expedite diagnosis and manage appropriately.

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