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# Placental Pathology in Maternal Ornithine Transcarbamylase Deficiency

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## Abstract

**Introduction:** Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder, inherited in an X-linked manner. Males are severely affected. Female phenotypes vary from asymptomatic to severe, and symptoms may be triggered by high metabolic states like childbirth. Literature on OTC deficiency in pregnancy and placental pathology is limited.
**Methods:** Pathology records were searched at a single referral center from 2000–2020 and identified three placental cases from two mothers heterozygous for OTC deficiency. Placental pathology and maternal and neonatal history were reviewed in detail.
**Results:** The placenta from one symptomatic mother carrying an affected male fetus showed widespread high-grade fetal vascular malperfusion (FVM) lesions of varying age. These lesions were not seen in the two placentas from the asymptomatic mother.
**Discussion:** In cases of symptomatic maternal OTC deficiency, our findings highlight the need for placental examination. Since thrombotic events in the placenta have the potential to associate with fetal and neonatal endothelial damage, a high index of suspicion for neonatal thrombosis may be warranted.

## Keywords

ornithine transcarbamylase deficiency, placental pathology, perinatal, pregnancy, inborn errors of metabolism, metabolic

## Introduction

There are over 700 types of inborn errors of metabolism which can be broadly subdivided into three categories based on the underlying defect. These include disorders related to disturbed transport or catabolism of complex endogenous molecules ("storage type"), defects in mitochondrial energy production ("energy deficiency type"), and congenital enzyme deficiency causing toxicity from upstream substrate accumulation ("intoxication type"). Urea cycle defects are an example of an "intoxication type" of inborn error.[1] Although all of these conditions are rare, ornithine transcarbamylase (*OTC*) deficiency is the most common of the urea cycle defects, with an incidence of around 1:14,000 live births.[2,3]

*OTC* deficiency is inherited in X-linked fashion, with males therefore more severely affected. It results from the deficiency of the enzyme *OTC* which converts ornithine to citrulline as part of the urea cycle in the liver, with resultant accumulation of ammonia and glutamine. Ammonia is a potent neurotoxin, can lead to encephalopathy and coma, and causes much of the symptomatology of *OTC* deficiency.[4] Prognosis in affected neonates is generally poor, especially in severely affected males.[1] Newborn screening (NBS) may identify the disorder, but in the United States testing varies according to state. Alabama does not include *OTC* deficiency in NBS panel.[5] Only 8 states test for *OTC* deficiency via NBS, with testing in 3 additional states likely to detect *OTC* deficiency as part of screening for another disorder.[6]

The spectrum of the female phenotypes varies from asymptomatic to severe, including neurologic and behavioral

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**Table 1.** Pregnancy Characteristics in Cases of Maternal Ornithine Transcarbamylase Deficiency.

| | Pre-pregnancy Control | Number of Antepartum Admissions | Prenatal Diagnosis | $NH_4$ Peak | $NH_4$ at Delivery | Mode of Delivery | Indication for Delivery | Other Complications |
|---|---|---|---|---|---|---|---|---|
| M1/P1 | Poor, required g-tube in childhood, multiple admissions for ↑$NH_4$ | 3 | Yes: amnio at 18.4 weeks, hemizygous c.788 A > G, pAsp263Gly (D263G) | 178 | 133 | Cesarean section | Preterm labor with non-reassuring fetal heart tones | Anemia, poor weight gain in pregnancy, FGR |
| M2/P1 and M2/P2 | No ↑$NH_4$ | U | No | U | U | Vaginal deliveries | U | U |
| M2/P3 | No ↑$NH_4$ | 0 | Yes: amnio, FISH with Xp11.4 microdeletion | 37 | 18 | Vaginal delivery | Elective induction of labor | Tobacco use, anxiety, depression, A2DM |
| M2/P4 | No ↑$NH_4$ | 0 | Yes: amnio (normal) | 40 | 40 | Vaginal delivery | Term labor | Tobacco use, anxiety, depression, A1DM, Hep C |

M = Mother; P = Pregnancy; U = Unknown; amnio = amniocentesis; DM = diabetes mellitus; N/A = not applicable; FISH = fluorescence in-situ hybridization; hep C = hepatitis C; FGR = fetal growth restriction; ↑$NH_4$ = hyperammonemia.

symptoms, which may be triggered by high metabolic states including childbirth.[7] With an intensive and multidisciplinary approach to intrapartum treatment, maternal sequelae can be minimized.[2,7,8]

The literature on maternal *OTC* deficiency in pregnancy is limited, consisting of isolated case reports and small series, collected in a recent systematic review of 36 reported cases to date.[9] The risk of maternal postpartum decompensation is a well-documented finding, typically occurring between 3–14 days after birth, possibly due to a combination of birth-related metabolic stress, removal of the nitrogen consuming placenta, and increased protein load after uterine involution.[7,8,10,11] *OTC* deficiency may be associated with a high rate of maternal morbidity and/or mortality, especially when not recognized prior to pregnancy.[9]

Although placental histopathology in certain "storage type" inborn errors of metabolism is well-described in the literature and textbooks,[12] descriptions of placental pathology in cases of "intoxication type" defects are lacking. We identified only one case of maternal symptomatic *OTC* carrier with mention of placental pathology, which was reported as "no evidence of chorioamnionitis" (and no mention of other pathology).[13] It is unclear whether the lack of reported pathology is due to a true lack of pathology, the rarity of these diseases, or both. Therefore, our objective was to report placental pathology findings from affected mother/baby dyads spanning 20 years from a single tertiary care center.

## Materials and Methods

The University of Alabama at Birmingham Institutional Review Board granted approval for these research activities-IRB #300007131. Perinatal pathology records at our institution were searched from inception of digital records (2000) to October 1, 2020. Three placental cases were identified, representing placental tissue from two mothers heterozygous for *OTC* deficiency, including a total of three births. We included all cases that resulted from our search and our search did not identify any female offspring with subtle placental findings. Placental tissue for all three cases was collected and examined fresh via standard macroscopic protocols at the time of delivery, and tissue was processed and stained with hematoxylin and eosin according to routine laboratory protocols for formalin fixed and paraffin embedded tissue. Standard Amsterdam criteria were followed for microscopic examination.[14]

### *Mother-Baby Dyad #1*

This is the first pregnancy of a 21-year-old G1P0 female with *OTC* deficiency diagnosed at 5 years old (Table 1). She is known to have a heterozygous pathogenic variant, c.788A>G (p.D263G) in the *OTC* gene. The patient had an extensive history of poor metabolic control requiring multiple hospitalizations due to hyperammonemia. The patient's pregnancy was confirmed at estimated 8–9 weeks gestation. She subsequently required inpatient admission secondary to hyperammonemia at the 11th, 15th, and 18th week gestation. Diagnostic amniocentesis was performed at 20 weeks gestation and the fetus was

**Table 2.** Neonatal Characteristics in Cases of Maternal Ornithine Transcarbamylase Deficiency.

| | Infant Sex | GA at Delivery | Apgar: 1 minute | Apgar: 5 minutes | Birth Weight (%ile) | Cord Gas | NICU stay (days) | $NH_4$ Level[a] | *OTC* Treatment | Neonatal Death | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M1/P1 | M | 34 6/7 | 2 | 9 | 1860 g (7th) | PH 7.15, $pCO_2$ 61.0, $HCO_3$ 21.4, BE-8 | 9 | 164 | IV nitrogen scavengers | Yes on DOL#9 | D263G variant *OTC* gene; pulmonary HTN, respiratory failure, oliguria, IVH, coagulopathy |
| M2/P1 | F | U | U | U | U | U | 0 | U | Admission for IVF in times of illness | No | Seizure disorder, Xp11.4 microdeletion[b] |
| M2/P2 | M | U | U | U | U | U | 0 | >1000 | Liver transplant | No | Xp11.4 microdeletion[b] |
| M2/P3 | M | 40 4/7 | 8 | 9 | 3540 g (65th) | PH 7.24, $pCO_2$ 57.7, $HCO_3$ 24.7, BE-4 | 55 | 97 | Liver transplant | No | Xp11.4 microdeletion[b] |
| M2/P4 | M | 38 | 9 | 9 | 3180 g (50th) | PH 7.24, $pCO_2$ 59.2, $HCO_3$ 25.1, BE-4 | 0 | U | None (not affected) | No | None |

[a]Normal Range 18–72 μmol/L.
[b]This microdeletion encompassed the entire *OTC* gene as well as five other genes.
U = Unknown; A = Affected; NA = Not Affected; M = Mother; P = Pregnancy; F = female; M = male; DOL = day of life; GA = gestational age; HTN = hypertension; IVH = intraventricular hemorrhage; NICU = neonatal intensive care unit; IVF = intravenous fluids; *OTC* = ornithine transcarbamylase deficiency.

confirmed to be a male affected with *OTC* deficiency. The fetus was monitored regularly with fetal ultrasounds, and fetal growth restriction was noted at 30 weeks gestation. At 34 6/7ths weeks gestation, a cesarean section was performed due to non-reassuring fetal heart tones obtained after she presented to the hospital with preterm contractions. Neonatal Apgar scores were 2 at 1 minute and 9 at 5 minutes (Table 2). Birth weight was 1860 g (seventh percentile), length 42 cm ($10^{th}$ percentile), and head circumference was 30 cm (sixth percentile). The infant's ammonia level at birth was 144 μmol/L (normal range: 18–72 μmol/L). He was admitted to the neonatal intensive care unit (NICU) where his ammonia level was controlled with intravenous nitrogen scavenger medications. His clinical course was complicated by pulmonary hypertension, respiratory failure, oliguria, intraventricular hemorrhage, and coagulopathy. Life support was withdrawn at 9 days of life. A neonatal autopsy was declined by the parents.

Placental examination revealed a weight of 535 g, which is large for estimated gestation (331–491 g expected; fresh, trimmed weight). The umbilical cord was trivascular with a normal eccentric insertion onto the chorionic plate, and was not hypercoiled (3 coils/10 cm of length). Umbilical cord coiling index (3 coils/10 cm of length) and total length received (63 cm), were near the upper limit of normal for gestational age (with recognition that the umbilical cord length may be underestimated, as any parts previously incised in the delivery room are not included in the total).[15,27] Microscopic examination revealed high-grade fetal vascular malperfusion (FVM) lesions of varying age, widespread and segmental in distribution, present in every sampled section. Multiple large stem villous and chorionic plate vessels showed nonocclusive thrombosis with focal mural calcification (Figure 1). Segmental swaths of remote distal villous sclerosis were present in all examined sections (Figure 2), and large regions were present showing distal villous capillary dissolution with acute intravillous hemorrhage (Figure 3).

## Mother #2

A 21 year old P2002 female with an Xp11.4 microdeletion which encompasses the entire *OTC* gene was referred to the maternal-fetal medicine clinic at a tertiary medical center at

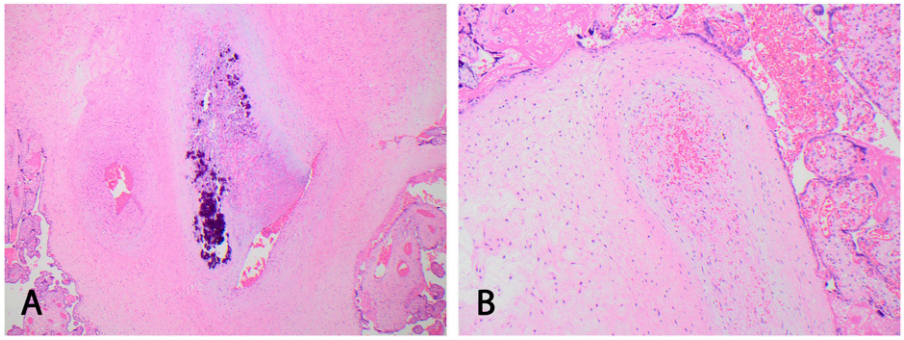


**Figure 1.** High grade fetal vascular malperfusion lesions. Multifocal nonocclusive thrombus and vascular endothelial breakdown with calcification, large stem villous and chorionic plate vessels, seen in all examined sections. (H&E; (A) – 4× and (B) – 10× magnification).

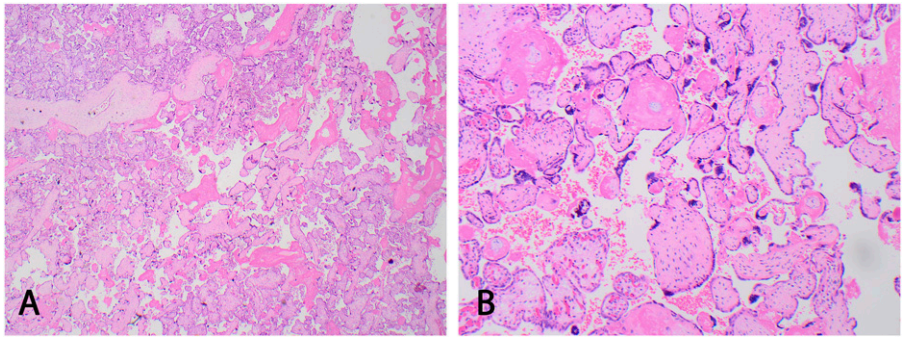


**Figure 2.** High grade fetal vascular malperfusion lesions. Multifocal segmental swaths of remote distal villous sclerosis, seen in all tissue sections. (H&E; (A) – 2× and (B) – 4× magnification).

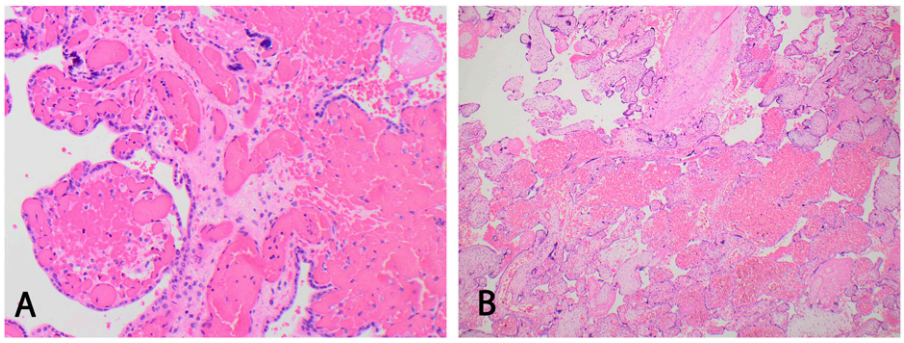


**Figure 3.** High grade fetal vascular malperfusion lesions. Multifocal regions of acute intravillous hemorrhage. (A) Admixture of acute intravillous hemorrhage (seen mostly lower half of image) and distal villous sclerosis (seen more in upper half of image) H&E 4×. (B) Higher power (H&E, 20×) view of intravillous hemorrhage and disintegration of capillary vascular profiles.

36 6/7 weeks estimated gestational age (EGA) due to the known chromosome microdeletion (Table 1). The patient had a history of learning disabilities and poor vision, but no known episodes of hyperammonemia or altered mental status. She was previously determined to be an obligate carrier of the Xp11.4 microdeletion after both a son and daughter were confirmed to have the microdeletion (Table 2). Her first affected son was born at an outside hospital via vaginal delivery when she was 19 years old. His growth parameters at birth were all within normal limits for a term infant. He then developed hyperammonemia (>1000 μmol/L) on the second day of life. Unfortunately, the only female offspring in our review belonged to this mother. She delivered this neonate at an outside hospital and thus we do not have placental pathology available from this birth or her affected son.

For the third pregnancy, maternal ammonia levels were monitored after she established care with Maternal–Fetal Medicine (MFM) and were normal. Diagnostic amniocentesis was performed at 37 4/7 weeks gestation and confirmed the fetus was a male who inherited the Xp11.4 microdeletion.

The pregnancy was further complicated by gestational diabetes, and the patient was subsequently induced at 40 4/7 weeks gestation due to gestational diabetes. Neonatal Apgar scores were 8 at 1 minute and 9 at 5 minutes. The birthweight was 3540 g (65$^{th}$ percentile), length was 51 cm (72$^{nd}$ percentile), and head circumference was 34 cm (36$^{th}$ percentile). The male offspring had a prolonged and complicated NICU course and a liver transplant was performed at 11 months of age.

The placenta from this delivery was large for estimated gestation, at the upper limits of normal (590 g; 409–589 g; trimmed, formalin fixed weight). The umbilical cord was trivascular with a normal eccentric chorionic plate insertion, and was not excessively long (46 cm received). Coiling pattern is unknown. Microscopic examination was remarkable only for mild acute subchorionitis without fetal inflammatory response. Patchy regions of chorionic villi showed subtle delay in villous maturation with some increase in capillary density. There was no evidence of fetal or maternal vascular malperfusion or other significant lesions.

The mother represented 1 year later at 22 weeks gestation to re-establish care in the MFM Clinic at our institution. Maternal ammonia levels were again monitored and were normal. Diagnostic amniocentesis was performed at 22 5/7 weeks which confirmed a male fetus that did not inherit the Xp11.4 microdeletion. The pregnancy was again complicated by gestational diabetes and newly diagnosed hepatitis C. The male offspring was delivered at 38 weeks EGA following spontaneous term labor. Neonatal Apgar scores were 9 at 1 minute and 9 at 5 minutes. The birthweight was 3180 g (50$^{th}$ percentile), length was 49.5 cm (50$^{th}$ percentile), and head circumference was 35.5 cm (90$^{th}$ percentile). He was discharged from the newborn nursery following routine newborn care.

The placenta was normal in weight (588 g; 442–632 g expected; fresh, trimmed weight), with a trivascular umbilical cord which was not excessively long (32 cm received). Insertion on the chorionic plate was normal eccentric. Coiling pattern was unknown. Microscopic examination was remarkable only for chorionic meconiophages. There was no evidence of fetal vascular malperfusion or other significant lesions.

## Discussion

To our knowledge, this is the first detailed report of placental pathology in mothers who carry the *OTC* gene. We describe placental findings in three placentas from live births to two mothers heterozygous for *OTC* mutations. The two placentas from the asymptomatic mother, one from an affected fetus and one from an unaffected fetus, had relatively normal pathology. The placenta from the mother with poorly controlled symptoms, carrying an affected male fetus, showed extensive fetal vascular malperfusion lesions. These lesions were characterized by large vessel thrombosis in stem villi and large swaths of downstream sclerosis of the distal villi (segmental, complete pattern of injury).

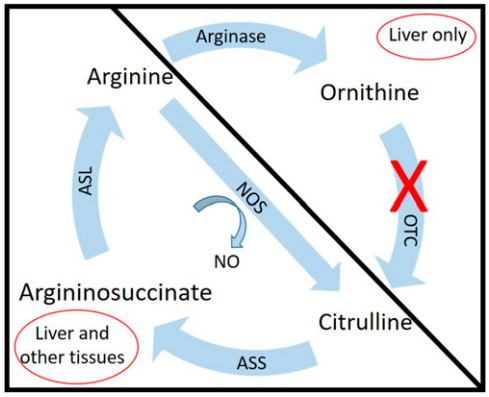


**Figure 4.** Urea cycle overview, showing ornithine transcarbamylase (OTC) deficiency in arginine metabolism and nitric oxide synthesis in liver and other tissues. ASL, Argininosuccinate lyase; ASS, Argininosuccinate synthase; NOS, Nitric Oxide Synthetase; OTC, Ornithine transcarbamylase.

The most common presumed etiology of flow problems causing placental fetal vascular malperfusion lesions is intermittent umbilical cord (UC) obstruction, excessive UC length or coiling, or abnormal insertion of the UC. Other risk factors have been reported, including fetal or maternal coagulopathy, or acute or chronic vasculitis as part of an inflammatory process.[16,17] In this series, none of the mothers had clinical suspicion for cord obstruction. Although the umbilical cord length and coiling were near the upper limit of normal in case #1 (a risk factor for FVM), symptomatic *OTC* deficiency raises suspicion for a metabolic cause for the placental findings. The FVM lesions seen in case #1 could be associated with a metabolic cause through symptomatic *OTC* deficiency, having an umbilical cord length and coiling index on the upper limits or normal, or a combination of both.

Endothelial cell metabolism is important in maintaining proper vascular function and flow, is an important mediator of angiogenesis during development.[18,19] Limited information is available on endothelial metabolism of the *fetal* circulatory component of the placenta. Recent in vitro studies have demonstrated that cellular responses and gene expression profiles in fetal placental endothelium vary with respect to ambient oxygen tension, with potential implications for the interplay of endothelial metabolism and angiogenesis.[20,21] In particular, investigations of placental vascular function have focused on the role of nitric oxide (NO) in mediating the effects of oxidative stress.[22,23] NO is produced from the essential amino acid arginine via nitric oxide synthetase (NOS) metabolism to citrulline. Although arginine metabolism via the full urea cycle only occurs in the liver, a separate pathway in liver and other tissues (including vascular endothelium) regenerates arginine via the enzymatic actions of argininosuccinate lyase (ASL) and argininosuccinate synthase (ASS) (Figure 4).

Two hypotheses arise from these observations and may help explain the histologic findings in the placenta from the symptomatic mother/baby dyad in this case. First, it is

possible that high ammonia levels in the fetal bloodstream could cause direct endothelial toxicity. In the case of mother/baby dyad #1, maternal hyperammonemia may have overwhelmed the placental capacity for detoxification, leading to increased fetal ammonia levels. Second, in the setting of poorly controlled *OTC* deficiency, arginine regeneration via ASS and ASL could decrease due to the decrease of citrulline precursor, leading to concomitant decreased production of NO, potentially resulting in vasoconstriction and abnormal fetal blood flow. There is some evidence for decreased systemic NO via this mechanism in animal models of *OTC* deficiency,[24] but not in human patients receiving exogenous arginine supplementation.[25] Theoretically, this could happen in the placenta either via systemic variation in NO levels or metabolism or as a component of localized endothelial arginine metabolism. These are subjects for further study.

FVM lesions, when severe, may be associated with poor fetal and/or neonatal outcomes including CNS damage. Of note, thrombotic events in the fetus or neonate have also been reported to associate with FVM of any cause.[16] In the setting of *OTC* deficiency, major thrombotic events have been reported in a series of four affected male infants (7 days old to 6 months old) with *OTC* deficiency. Low arginine levels were observed in all of these patients at the time of thrombosis. It was thought that given arginine's important role in NO homeostasis, that NO deficiency could cause endothelial dysfunction contributing to an increased thrombotic risk for these patients. Placental pathology for these cases was not mentioned in the report, nor was maternal status.[26]

In cases of symptomatic maternal *OTC* deficiency with an affected fetus, particularly when poorly controlled, our findings highlight the need for placental examination. It is possible that the long cord and the *OTC* deficiency, together, resulted in thrombosis. Because thrombotic events in the placenta have the potential to associate with fetal and neonatal endothelial damage, a high index of suspicion for neonatal thrombosis should be maintained.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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