



Published in final edited form as:

Obstet Gynecol Clin North Am. 2018 June ; 45(2): 249–265. doi:10.1016/j.ogc.2018.01.010.

Maternal Genetic Disorders in Pregnancy

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Keywords

Pregnancy; Management; Genetic disorders; Hereditary hemorrhagic telangiectasia; Tuberous sclerosis; Myotonic dystrophy; Ornithine transcarbamoylase deficiency

INTRODUCTION

As the life expectancy and quality of life improves for individuals with genetic conditions, so does the need for information regarding the management of reproductive issues. A recent review article addressed pregnancy care in women with some of the more common genetic conditions, including phenylketonuria, Turner syndrome, cystic fibrosis, connective tissue disorders, and disorders of fatty oxidation.¹ The authors, therefore, focus their review on pregnancy management and outcomes in women with hereditary hemorrhagic telangiectasia (HHT), tuberous sclerosis complex (TSC), myotonic dystrophy, and ornithine transcarbamoylase (OTC) deficiency.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant multisystem disease leading to the development of multiple arteriovenous malformations (AVMs). AVMs are abnormally formed vessels that lack capillaries, resulting in a direct connection of an artery with a vein. HHT is estimated to occur in approximately 1 in 5000 individuals.²

HHT is caused by mutations in genes that encode proteins for the transforming growth factor-beta (TGF- β) signaling pathway, which is involved in angiogenesis.³ It is estimated that 75% of patients who meet the clinical criteria for the diagnosis of HHT will have an identifiable mutation in one of 3 genes, *ACVRL1*, *ENG*, *SMAD4*.⁴ Additional genes, including *GDF2*, are being investigated for their role in the pathogenesis of HHT.⁵ Molecular genetic testing is available to establish a genetic diagnosis in clinically suspected cases.

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Disclosure Statement: The authors have no conflicts of interest.

The presentation of HHT is highly variable. Small AVMs, also called telangiectasia, can be found on the fingers, face, nasal mucosa, lips, tongue, and gastrointestinal mucosa.³ Telangiectasias can range from small, blanchable, pink to red lesions to large, raised, purple lesions. Because of the abnormal formation of the vessels and the close proximity to the skin surface, telangiectasias can rupture and bleed.³ The most common presenting symptom is recurrent episodes of epistaxis, occurring in more than 95% of patients. Large AVMs can also occur within the lungs, liver, or brain. The major concern with HHT is the risk of spontaneous rupture of a large AVM leading to a catastrophic bleed.³

HHT is typically a clinical diagnosis, for which diagnostic criteria have been developed⁶ (Table 1). Current management guidelines recommend that individuals with HHT undergo screening for vascular malformations at the time of diagnosis, including MRI with and without contrast for the detection of cerebral AVMs, transthoracic contrast echocardiography for the detection of pulmonary AVM with follow-up for abnormalities with unenhanced thoracic computed tomography (CT), and liver ultrasound or abdominal CT for the detection of liver vascular malformations.⁷

Pregnancy in Women with Hereditary Hemorrhagic Telangiectasia

Fertility is not typically affected, and no increased risk of miscarriage has been reported in women with HHT.⁸ Most pregnancies are uneventful. However, pregnancies in women with HHT should be considered high risk given the possibility of significant morbidity and mortality associated with the risk of bleeding from AVMs.

An increase in development of new skin and mucosal telangiectasias has been reported in some women. The frequency of episodes of epistaxis may increase during pregnancy; however, these episodes are not typically associated with significant complications.⁹

A significant increase in pregnancy complications has been reported in women with pulmonary AVMs (PAVMs).¹⁰ The abnormal, dilated vessels can create a right-to-left shunt between the pulmonary arterial and venous systems, which leads to arterial hypoxemia and an increased risk of ischemic and paradoxical embolic events.¹¹ PAVMs can also rupture leading to massive hemoptysis.

One retrospective series of 161 pregnancies in 47 women reported 6 cases of worsening right-to-left intrapulmonary shunting evident by increased hypoxemia and worsening dyspnea, 2 maternal deaths secondary to PAVM hemorrhage, and 3 strokes.⁸ A second study including retrospective and prospective data of 484 pregnancies in 199 women reported life-threatening complications in 13 pregnancies, including 6 PAVM hemorrhages, 6 strokes, and 1 myocardial infarction. There were 5 maternal deaths. A statistically significant improvement in survival for women diagnosed with HHT or PAVM before pregnancy was noted.¹² In a separate study of 244 pregnancies in 87 women with HHT, 7 complications secondary to PAVMs were reported, including hemothorax, transient ischemic attack (TIA), myocardial infarction, and myocardial ischemia. Notably, all of the complications occurred in women who had not had screening or been treated for PAVMs. Most complications related to PAVMs have been reported in the second or third trimester, likely due to the increased maternal blood volume and cardiac output.⁹

Although cerebral AVMs (CAVMs)¹³ and hepatic AVMs¹⁴ are more prevalent in women with HHT, the risk of associated pregnancy complications seems to be low with only a few case reports in the literature.^{8,12} Women who have had a previous CAMV rupture may be at increased risk for rebleeding during the second and third trimester of pregnancy. Spinal cord AVMs are rare in HHT⁷; however, some providers are hesitant to provide local anesthesia during labor given concern for potential spinal involvement.⁹

Pregnancy Management

Pregnancies in women with HHT should be managed by a multidisciplinary team, including obstetricians, pulmonologists, neurovascular specialists, anesthesiologists, and interventional radiologists. Consensus guidelines for the management of pregnant patients with HHT are not available. Clinical management guidelines based on expert opinion have been suggested.¹² Pregnancy-related risks and management recommendations for women with HHT are outlined in Table 4.

Severe epistaxis can lead to iron-deficient anemia. Conservative management for epistaxis includes the use of humidifiers and nasal lubricants. Refractory cases may require additional procedures.⁷

Recommendations for screening asymptomatic patients during pregnancy vary. Some experts stress that screening should be completed before conception to optimize outcomes and that asymptomatic patients should not undergo screening during pregnancy.¹² However, as some patients present for the first time during pregnancy, it may be necessary to offer additional screening. de Gussem and colleagues⁹ suggest screening in the early second trimester with arterial blood gas analysis and transthoracic contrast echocardiography with follow-up chest CT for abnormal findings. If significant pulmonary AVMs are identified on CT, they recommend limited pulmonary angiography with embolization. Women with small AVMs are followed with arterial blood gas analysis in the second and third trimester to monitor for worsening hypoxemia, which would prompt a CT and treatment if indicated.

Screening for cerebral AVMs with MRI can be considered in the second or third trimester or delayed until after delivery. Delivery management for women identified to have a CAVM should be made in consultation with a neurosurgeon. Some experts argue that spinal AVM should be excluded by MRI.¹² However, others suggest MRI screening should be optional and that local anesthesia should be considered on a case-by-case basis given the low incidence of spinal AVMs in patients with HHT.⁹

Risk Assessment and Genetic Counseling

HHT is inherited in an autosomal dominant manner. Therefore, the offspring of an affected parent have a 1 in 2 (50%) chance of inheriting the condition. HHT is a highly variable condition, even within families, making it difficult to predict the phenotype prenatally.⁷

Prenatal and preimplantation genetic testing are technically feasible if a mutation has been identified in the family. However, the decision to undergo prenatal genetic testing is very personal and should be based on each individual patient's goals. Patients should be referred for formal genetic counseling to discuss the benefits and limitations of genetic testing.

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is an autosomal dominant, highly variable, multisystem disease involving the skin, brain, kidney, heart, and lungs. The condition is characterized by the growth of benign lesions that can disrupt normal functions leading to an increased risk of seizures, arrhythmias, renal failure, and lung disease. TSC occurs in approximately 1 in 6000 to 1 in 10,000 livebirths.¹⁵

Approximately 75% to 90% of patients with TSC will have a mutation in the *TSC1* or *TSC2* gene.¹⁶ Hamartin and tuberin are the gene products of *TSC1* and *TSC2*, respectively. The two proteins form a heterodimer and control cell growth and proliferation through inhibition of the mammalian target of rapamycin (mTOR) pathway.¹⁷ Mutations in the *TSC2* gene tend to be associated with a more severe phenotype, including younger age at presentation, seizures, and intellectual disability.¹⁸

Given the highly variable nature of this disease, diagnosis can be challenging. Diagnostic criteria have been developed based on genetic testing and the presence of major or minor criteria⁶ (Table 2). TSC demonstrates age-dependent manifestations. In infancy and childhood, individuals are more likely to present with cardiac rhabdomyomas, brain hamartomas, and seizures. Characteristic skin lesions and TSC-associated neuropsychiatric disorders, including autism spectrum disorders, intellectual disabilities, psychiatric disorders, and neuropsychological deficits, may present throughout patients' lifetime. However, renal manifestations, such as angiomyolipomas, and the lung disease, lymphangioleiomyomatosis (LAM), are more likely to present in adulthood.¹⁵

mTOR inhibitors are a new oral medication that have been shown to reduce the growth of TSC-associated lesions. They are now considered the first-line therapy for asymptomatic angiomyolipomas measuring greater than 3 cm in diameter and can be used in patients with LAM who have moderate to severe lung disease.¹⁹

Pregnancy in Women with Tuberous Sclerosis Complex

Patients with TSC with a high disease burden, including those with significant TSC-associated neuropsychiatric disorders, may not reproduce. However, the phenotypic spectrum of TSC varies and can also present with milder features that are less life limiting. There are case reports of women diagnosed with TSC only after the birth of affected children.²⁰ Current publications of pregnancy in women with TSC are limited to case reports and literature reviews.

King and Stamilio²⁰ completed a systematic review of TSC in pregnancy. They identified 23 pregnancies in 17 women with TSC. Complications were noted in 10 out of 23 (43%) pregnancies, including preeclampsia, oligohydramnios, polyhydramnios, intrauterine growth restriction, hemorrhage from ruptured angiomyolipomas, premature rupture of membranes, renal failure, placental abruption, and perinatal demise. Perinatal complications were found in all five of the women who had TSC-associated renal disease. No maternal deaths were reported. The authors concluded that pregnancies in women with TSC are at high risk for adverse outcomes.

Angiomyolipomas and LAM are 2 findings in TSC that can be associated with adverse outcomes in pregnancy. Angiomyolipomas are benign mesothelial tumors made up of mature adipose tissue, blood vessels, and smooth muscle cells that are observed in 80% of TSC patients.¹⁶ They are typically asymptomatic, but can present with abdominal pain, hypotension, and shock secondary to rupture. It has been suggested that there is an increased risk of rupture during pregnancy.²¹ LAM is a rare cystic lung disease that affects up to 80% of women with TSC.²² It is characterized by smooth muscle cells infiltrating and destroying normal lung tissue. Patients typically present with dyspnea on exertion and multiple pneumothoraces.¹⁶ It has been suggested that LAM may worsen during pregnancy secondary to the effects of estrogen.²³

Fetuses affected with TSC are also at an increased risk for complications. Cardiac rhabdomyomas can be a presenting feature in TSC and may be diagnosed prenatally. Although many rhabdomyomas will regress postnatally, they are associated with fetal dysrhythmias and the development of hydrops. In one case series of 37 cases of fetal cardiac rhabdomyomas associated with TSC, there were 6 cases of perinatal demise that were all preceded by in utero hydrops.²⁰

Pregnancy Management

Consensus guidelines of the management of individuals with TSC do not provide guidance for pregnancy management.¹⁹ Pregnancy management should include a multidisciplinary team given the multisystem nature of TSC and may include obstetrics, nephrology, neurology, pulmonology, intervention radiology, and anesthesiology. Pregnancy-related risks and management recommendations for women with TSC are outlined in Table 4.

In individuals with TSC, angiomyolipomas should be monitored every 1 to 3 years by MRI and renal function and blood pressure should be checked annually.¹⁹ There are no specific recommendations for screening for angiomyolipomas during pregnancy. A ruptured angiomyolipoma should be high on the differential for pregnant women with TSC who present with acute-onset abdominal pain, hypotension, or shock. The first-line treatment of hemorrhaging angiomyolipoma is embolization followed by corticosteroids.¹⁹ Referral to nephrology should be made if renal dysfunction is noted. Continued follow-up with nephrology postpartum is indicated, as patients with renal lesions associated with TSC are at risk of developing renal failure.

TSC management guidelines do not make recommendations on screening for LAM during pregnancy; however, it is recommended that asymptomatic patients have screening with high-resolution CT (HRCT) every 5 to 10 years.¹⁹ Pregnant women who present with worsening dyspnea or recurrent pneumothoraces may need further evaluation, imaging, and referral to a pulmonologist.

Medications used to treat TSC may not be safe in pregnancy. mTOR inhibitors are a relatively new class of medication, so teratogenic effects are not well established. There are case reports of normal fetal outcomes, but the number of pregnancies limit the ability to generalize these results.²⁴ Certain antiepileptic medications are known to be associated with an increased risk for congenital anomalies, including open neural tube defects and cardiac

anomalies.²⁵ Reviewing all medications before conception or early in pregnancy is recommended.

Targeted anatomic survey and fetal echocardiogram is warranted to evaluate for cardiac rhabdomyoma, which would be diagnostic of fetal TSC. Fetuses diagnosed with cardiac rhabdomyoma should have increased surveillance given the increased risk for the development of hydrops.²⁶ Weekly ultrasounds to screen for hydrops can be considered after a diagnosis of a fetal cardiac rhabdomyoma. The optimal gestational age to begin screening for hydrops depends on the family's wishes for intervention and resuscitation. Fetal MRI can be considered to further evaluate for brain lesions. Fetuses identified to have significant brain findings may be at an increased risk of seizures and intellectual disability. Prenatal consultation with a pediatric neurologist can be considered for a discussion of prognosis.

Risk Assessment and Genetic Counseling

Approximately 66% of cases of TSC result from a de novo mutation; of those that are inherited, TSC demonstrates an autosomal dominant pattern of inheritance.¹⁵ Women with TSC have a 50% (1 in 2) chance of passing on the condition to their offspring.

Preimplantation genetic diagnosis and prenatal diagnosis with chorionic villus sampling (CVS) or amniocentesis is available if the mutation has been detected in the family. As discussed previously, imaging studies can also evaluate for features suggestive of TSC in the fetus. Fetal cardiac rhabdomyoma is diagnostic for fetal TSC in an at-risk pregnancy. Patients should be referred to genetic counseling to review the available testing options.

MYOTONIC DYSTROPHY

Myotonic dystrophy is an autosomal dominant multisystem neuromuscular disorder associated with slowly progressive muscle weakness and myotonia, or sustained muscle contractions. There are 2 types of myotonic dystrophy, myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2). For this review, the authors focus on DM1, as it is the most common form of muscular dystrophy affecting pregnant women.²⁷ It is estimated that DM1 has a prevalence of between 3 and 10 per 100,000 live births.²⁸

DM1 is a triplet repeat disorder caused by expansion of CTG repeats in the 3' untranslated region of the *DMPK* gene. The diagnosis of DM1 is based on the finding of repeat length greater than 50 CTGs. Genotype-phenotype correlations have been established with larger repeat lengths associated with an earlier age of onset and a more severe clinical presentation (Table 3).²⁹ DM1 also demonstrates anticipation, with more significant clinical disease in successive generations due to expansion of CTG repeats. The most severe presentation, congenital myotonic dystrophy, is almost exclusively due to a maternally inherited repeat expansion.³⁰

The clinical features of DM1 are variable and described along a continuum of 3 major types based on repeat length (see Table 3): mild, classic, and congenital.²⁹ Patients with mild DM1 typically have cataracts and mild myotonia with a normal life span. Patients with classic DM1 have cataracts, muscle weakness, myotonia, and cardiac conduction abnormalities.

This type can be associated with physical limitations and a shortened life span. Congenital DM1, the most severe presentation, is characterized by severe generalized weakness, hypotonia, and respiratory insufficiency at birth. It is also associated with intellectual disability and early death.³¹

Pregnancy in Women with Myotonic Dystrophy Type 1

Pregnancies in women with DM1 are considered to be high risk. Women with classic DM1 are more likely to have pregnancy complications than women with mild disease.³² Available information regarding pregnancy outcomes is limited to small retrospective case series and literature reviews.

Two case series of women with DM1 reported that rates of miscarriage were not increased over the background population risk.^{32,33} A registry-based study reported a higher rate of miscarriages (32.0% vs 16.9%) in women with DM1 as well as increased use of assistive reproductive technology, as compared with the general population.³⁴ Ectopic pregnancies were increased in one case series, which may represent impaired tube mobility.³²

An increased rate of severe urinary tract infections during pregnancy has been noted, with rates between 9%³³ and 13%³² of pregnancies. Some experts have hypothesized that this may be secondary to subtle pelvic floor muscle weakness in women with DM1.³⁵

Polyhydramnios has been reported with a frequency of 10% to 20% but is exclusively seen in pregnancies affected by congenital myotonic dystrophy secondary to impaired fetal swallowing. Higher rates of stillbirth and neonatal deaths³² are also attributed to fetuses affected with congenital myotonic dystrophy.

Uterine muscle abnormalities have been suggested as a cause of pregnancy complications in women with DM1. An increased risk for placenta previa and abnormal vaginal bleeding has been noted, with a 10-fold increase more than the general population.^{32,33} Prolonged labor due to uterine dysfunction and maternal weakness has been implicated as the reason for an increased rate of cesarean deliveries, instrumental deliveries, and nonvertex presentations. Increased rates of postpartum hemorrhage due to uterine atony or abnormal placentation have also been reported.^{32,33}

Preterm birth, defined as delivery before 37 weeks' gestation, is more common in women with DM1 with rates reported at 34%,³² 36.7%,³³ and 31%³⁴ compared with the baseline US population risk of 10%. Rudnik-Schöneborn and Zerres³² reported that 15% to 20% of pregnancies delivered before 34 weeks' gestation, late preterm deliveries (34–37 weeks' gestation) occurred in about one-third of births, and only about half reached full term (after 37 weeks' gestation).

Johnson and colleagues³⁴ conducted a registry-based study to investigate the impact of pregnancy on women with myotonic dystrophy. Women with DM1 reported a significant increase in the impact of mobility limitations, activity limitations, pain, emotional issues, and myotonia from before pregnancy to after pregnancy. Although these results may suggest that pregnancy may lead to disease progression, this study relied on retrospective data and

there was selection bias based on a low response rate of women with DM1 recruited through patient registries.

Pregnancy Management

The European Neuromuscular Center published recommendations for the management of pregnancy in women with neuromuscular disorders, including DM1.³⁶ They stress the importance of a multidisciplinary approach to the care of these women, which should include providers in obstetrics, neurology, anesthesiology, and genetics. Pregnancy-related risks and management recommendations for women with DM1 are outlined in Table 4.

Women with DM1 should plan to receive prenatal care and deliver at tertiary care centers given the increased risk for abnormal placentation, labor abnormalities, and complicated urinary tract infections. Additionally, some women with DM1 may have some associated cognitive delays that may limit their ability to understand risks, so close medical guidance is important.³²

DM1 is associated with an increased risk for conduction disorders and arrhythmias, although the risk seems to be higher in men. A 2012 meta-analysis assessing the cardiac risks in patients with DM1 reported the risk for sudden cardiac death to be 0.56% per year.³⁷ Given this risk, echocardiogram and electrocardiogram screening may be warranted in pregnancy.³²

Consultation with anesthesia is warranted for patients with significant muscle weakness to allow thoughtful planning for anesthetic needs during labor and delivery. Patients with DM1 may be at an increased risk for aspiration, excessive response to anesthetics, and increased myotonia with certain anesthetic agents.³⁸

Risk Assessment and Genetic Counseling

DM1 is inherited in an autosomal dominant pattern. Offspring of affected individuals have a 50% (1 in 2) chance of inheriting the abnormal gene. An expanded DMPK gene has the potential to expand further during gametogenesis, resulting in children with earlier onset and more severe disease.³⁹ As noted previously, maternal transmission of the expansion of repeats may lead to congenital myotonic dystrophy. Cobo and colleagues⁴⁰ reported that the risk of congenital myotonic dystrophy increased with repeat length. Women with a CTG repeat less than 300 had a 10% risk of having a child with congenital myotonic dystrophy, whereas women with CTG repeat greater than 300 had a 59% risk for having an affected child.

Genetic testing for DM1 can be completed with prenatal genetic testing of the *DMPK* gene through CVS or amniocentesis. Preimplantation genetic testing is also an option for patients. Women with DM1 should be referred for genetic counseling to review the risks and testing options. Polyhydramnios and reduced fetal movement is suggestive of a diagnosis of congenital DM1 in an at-risk pregnancy.

ORNITHINE TRANSCARBAMOYLASE DEFICIENCY

Ornithine transcarbamylase deficiency (OTC) deficiency is an X-linked urea cycle disorder, a group of disorders caused by enzyme deficiencies that prevent the appropriate conversion of waste nitrogen to urea, leading to accumulation of toxic ammonia. In the most severe cases, urea cycle disorders present as encephalopathy and coma secondary to hyperammonemia.⁴¹ OTC deficiency is the most common of the urea cycle disorders and is caused by a deficiency of the enzyme OTC (Fig. 1). Recent estimates suggest the overall birth prevalence for urea cycle disorders in the United States is 1 in 35,000 and for OTC deficiencies the birth prevalence was estimated at 1 in 63,000 live births.⁴¹

OTC deficiency is caused by mutations in the *OTC* gene, which is located on the X-chromosome. Severe OTC deficiency typically affects boys who present within the first week of life with hyperammonemic coma. Milder symptoms or later age of presentation can also be seen in boys with partial enzyme activity.⁴² Presenting 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. It has been hypothesized that the degree of symptoms is related to the level of skewed X-inactivation within the liver.⁴³ Catabolic states, which lead to an increase breakdown of protein and nitrogen release, cause elevated levels of ammonia. Various triggers have been implicated for hyperammonemic episodes in female carriers of OTC deficiency, including infection, surgery, trauma, decreased oral intake, and high protein intake. Symptomatic female carriers are typically treated with low-protein diets with amino acid supplementations in addition to sodium benzoate to assist with nitrogen excretion.

Pregnancy in Female Carriers of Ornithine Transcarbamoylase Deficiency

Most female carriers of OTC deficiency have uneventful pregnancies. However, they are at risk of hyperammonemic episodes during times of catabolic stress, including labor and delivery and the postpartum period. Data regarding pregnancies in women with OTC deficiency are limited to single case reports, small case series, and literature reviews.

Most studies suggest that the period associated with the highest risk for acute decompensation is between postpartum day 3 and 14.⁴⁴⁻⁴⁶ Although the exact cause of postpartum hyperammonemia is not well understood, it is hypothesized that it may be secondary to increased protein catabolism that occurs with involution of the uterus.⁴⁶ Arn and colleagues⁴⁵ first reported adverse outcomes in women with OTC deficiency. Their case series included 2 known OTC carriers and one previously healthy woman who all developed hyperammonemic comas between postpartum days 3 and 8. Two of the women died secondary to cerebral edema. Many of the original case series are likely biased toward adverse outcomes.

Pregnancy is thought to be protective against the effects of hyperammonemic episodes secondary to the increased nitrogen needs of the placenta and fetus.⁴⁴ However, there have been case reports of hyperammonemic crisis in pregnancy. Schimanski and colleagues⁴⁷

reported the case of a previously healthy woman who presented with confusion and hyperemesis gravidarum at 14 weeks' gestation. Given concerns for malnutrition, she was treated with total parenteral nutrition (TPN) and 3 days later developed signs of encephalopathy and coma and subsequently died. The investigators conclude that the high protein load from TPN triggered the hyperammonemic episode. Lipskind and colleagues⁴⁸ reported the case of a known OTC carrier who was treated with corticosteroids for presumed preterm labor and subsequently became unresponsive and was found to be hyperammonemic. The investigators speculated that the corticosteroids in addition to low oral intake triggered an endogenous breakdown of protein, leading to hyperammonemia. The patient was treated with benzoate and a protein-restricted diet and her condition improved.

Maestri and colleagues⁴⁹ reported on a series of 175 women from 89 families with a family history of OTC deficiency. In their cohort, they identified 76 female carriers of OTC deficiency. Female carriers were more likely to report protein-restricted diets. Four women reported a personal history of coma, none of which occurred during the peripartum period. Among the 76 carriers, there were 260 pregnancies reported with no significant differences in fertility, number of miscarriages, or complications in pregnancies compared with the noncarrier women. However, limited data are presented about pregnancy outcomes. The investigators concluded that hyperammonemic encephalopathy is an uncommon finding in asymptomatic carriers of OTC deficiency but stressed the importance of educating women of this potential complication during times of physiologic stress.

Langendonk and colleagues⁵⁰ reported on a series of pregnancies in women with inborn errors of metabolism, including one full-term pregnancy in a woman with known OTC deficiency. The patient was treated with a protein-restricted diet with amino acid supplementation, sodium benzoate 6 g daily, citrulline 5 g daily, calcium 500 mg daily, folic acid 1 mg daily, and vitamin B6 100 mg daily and low-molecular-weight heparin. She reportedly had several episodes of elevated ammonia levels without significant clinical sequelae during pregnancy, triggered by a respiratory tract infection and nonadherence to her protein-restricted diet and amino acid supplementation. Her supplements were adjusted and her ammonia levels stabilized. She had mild hyperammonemia on postpartum day 1 and 3 and a sudden increase in ammonia at postpartum day 11, which was associated with agitation. She was treated with sodium benzoate and protein restriction and made a complete recovery. Additional case reports of women with known OTC deficiency carrier status have shown favorable outcomes when ammonia levels are monitored, allowing for early treatment and avoidance of a hyperammonemic coma.^{44,46,51} These cases highlight the importance of a well-established management plan.

Pregnancy Management

Guidelines for the management of pregnancy in female carriers are based on expert opinion. Pregnancies in female carriers of OTC deficiency should be managed by a multidisciplinary team, including obstetricians, geneticists, metabolic dieticians, and anesthesiologists. Pregnancy-related risks and management recommendations for women with OTC deficiency are outlined in Table 4.

Patients should have serum ammonia levels and plasma amino acids drawn at the time of routine prenatal laboratory tests. Women should also be counseled on the importance of adequate nutrition to avoid increased catabolism.⁴⁶ Women who have significant nausea and vomiting or infections leading to decreased oral intake may require more regular monitoring of ammonia levels.

Women with OTC deficiency tend to be on protein-restricted diets, which can increase the risk of fetal growth restriction. Formal evaluation by a metabolic dietician is warranted for women who have a challenge meeting appropriate oral intake goals.⁵² Increased antenatal surveillance is warranted if fetal growth restriction is identified.

The use of maintenance fluids, specifically 10% dextrose, has been recommended during labor and delivery given the increased energy demands.⁵² Some experts recommend checking plasma ammonium levels every 6 hours during the hospital course, with increased frequency if levels are abnormal.⁴⁶

Therapy should be initiated when ammonium levels are 1.5 to 2.0 times greater than normal and should be completed in consultation with an expert in urea cycle disorders. Mendez-Figueroa and colleagues⁴⁶ recommend oral sodium benzoate at 5 g/m²/d divided in 3 doses. Intravenous (IV) sodium phenyl-acetate and sodium benzoate at 5.5 g/m²/d with IV arginine at 3.5 g/m²/d in 24 hours should be initiated if patients are not tolerating oral intake or if ammonia levels are rapidly increasing. Hemodialysis may be required if the ammonia levels do not decrease or rapidly increase to greater than 250 mg/dL.

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.

Risk Assessment for Offspring and Potential Prenatal Testing Options

OTC deficiency is inherited in an X-linked manner. A female carrier has a 50% (1 in 2) risk of passing the mutated gene to her offspring. Male children who inherit the mutation will be affected, whereas female children may develop symptoms or may remain asymptomatic. Affected male infants with severe OTC deficiency appear normal at birth but present within the first days of life with lethargy leading to a hyperammonemic coma. Surviving infants are at an increased risk for developmental delays and often require liver transplantation.⁴¹ Individuals with partial OTC deficiency, which can include males and females, may present with hyperammonemic episodes from infancy to adulthood.⁵³

Preimplantation genetic diagnosis or prenatal genetic testing through CVS or amniocentesis are available when the mutation has been identified in the family. Women should be referred for genetic counseling to review available testing options.

SUMMARY

Improvements in medical care for women with genetic disorders has led to an increased number of women reaching reproductive age. Preconception counseling regarding pregnancy-associated risks and genetic testing options should be made available to all women with genetic disorders.

Outcomes of pregnancies in rare genetic conditions are mainly limited to case reports, small case series, and literature reviews. Although these publications provide valuable information to obstetricians caring for women with genetic disorders, additional research is needed to better characterize pregnancy outcomes. Patient registries and continued publications of cases are needed to allow for the development of pregnancy management guidelines.

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KEY POINTS

- Multidisciplinary management of pregnancy in women with genetic disorders is recommended.
- Discussions of maternal and fetal risks associated with pregnancy in women with genetic disorders, including options for genetic testing, are best completed before conception.
- Continued research of pregnancy outcomes in women with genetic disorders is needed.

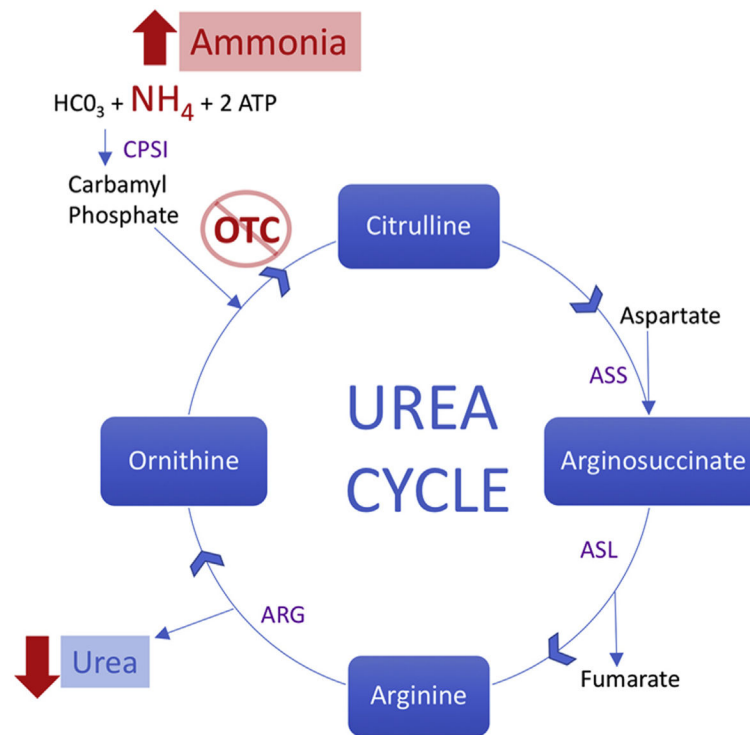


Fig. 1. OTC deficiency: a urea cycle disorder. The urea cycle is the metabolic pathway responsible for detoxification of excess and waste nitrogen. With each turn of the cycle, 2 nitrogen atoms are converted to urea, which can be safely excreted by the kidneys. Deficiency of the OTC enzyme, which catalyzes the production of citrulline from ornithine and carbamyl phosphate, prevents the formation of urea and leads to an accumulation of ammonium (NH_4). Systemic alkalosis converts NH_4 to the more toxic form, ammonia (NH_3). High levels of NH_3 are toxic to the brain and lead to the symptoms seen in OTC deficiency, including confusion, brain edema, and coma. ARG, arginase; ASL, argininosuccinate lyase; ASS, argininosuccinate synthase; CPSI, carbamoyl-phosphate synthase 1; HCO_3^- , bicarbonate.

Table 1

The Curaçao criteria

Diagnostic criteria for HHT	
<i>Definite diagnosis:</i> 3 criteria present	
<i>Possible or suspected diagnosis:</i> 2 criteria present	
<i>Unlikely:</i> <2 criteria present	
<hr/>	
Criteria	
<hr/>	
• Epistaxis	Spontaneous, recurrent nose bleeds
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• Telangiectasias	Multiple, at characteristic sites
	<ul style="list-style-type: none"> • Lips • Oral cavity • Fingers • Nose
<hr/>	
• Visceral lesions	Gastrointestinal telangiectasias
	Pulmonary AVM
	Hepatic AVM
	Cerebral AVM
	Spinal AVM
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• Family history	First-degree relative with HHT

From Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler Weber syndrome). Am J Med Genet 2000;91(1):67; with permission.

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Table 2

Diagnostic criteria for tuberous sclerosis complex

Genetic diagnostic criteria	
Identification of a pathogenic mutation in <i>TSC1</i> or <i>TSC2</i> is sufficient to make a definitive diagnosis of TSC	
Clinical diagnostic criteria	
Definite diagnosis: 2 major features or 1 major feature with >2 minor features	
Possible diagnosis: either 1 major feature or 2 minor features	
Major features	<ul style="list-style-type: none"> • Hypomelanotic macules (3, at least 5-mm diameter) • Angiofibromas (3) or fibrous cephalic plaque • Ungual fibromas (2) • Shagreen patch • Multiple retinal hamartomas • Cortical dysplasias • Subependymal nodules • Subependymal giant cell astrocytoma • Cardiac rhabdomyoma • Lymphangiomyomatosis • Angiomyolipomas (2)
Minor features	<ul style="list-style-type: none"> • Confetti skin lesions • Dental enamel pits (>3) • Intraoral fibromas (2) • Retinal achromic patch • Multiple renal cysts • Nonrenal hamartomas

Adapted from Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol* 2013;49(4):244; with permission.

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Table 3

Genotype-phenotype correlations in myotonic dystrophy type 1

Phenotype	Clinical Features ^a	CTG Repeat Length
Normal (unaffected)	None	5–34
Premutation	None	35–49
Mild	Cataracts Mild myotonia	50–150
Classic	Weakness Myotonia Cataracts Cardiac arrhythmia	100–1000
Congenital	Infantile hypotonia Respiratory difficulties Intellectual disability	>1000

^aThere is significant overlap of phenotypes and CTG repeats, making predictions of age of onset and severity for individual patients challenging.

Data from The International Myotonic Dystrophy Consortium (IDMC). New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). *Neurology* 2000;54(6):1218–1221.

Table 4

Risks and management recommendations for specific genetic disorders

Genetic Condition	Pregnancy-Related Risks	Management Recommendations
HHT	<ul style="list-style-type: none"> • Increased episodes of epistaxis • Development of new skin and mucosa telangiectasias • Increased risk of hemorrhage from pulmonary AVMs 	<p>Recommendations based on expert opinion^{9,12}</p> <ul style="list-style-type: none"> • PAVMs <ul style="list-style-type: none"> – Preconception screening with chest CT and treatment if indicated – Consider screening during pregnancy, if no previous screening completed – Educate patients on concerning signs or symptoms, including hemoptysis and sudden, severe dyspnea • Cerebral AVM <ul style="list-style-type: none"> – Cerebral MRI for women with family history of cerebral hemorrhage or symptoms – No asymptomatic screening during pregnancy • Spinal AVM <ul style="list-style-type: none"> – Consider spinal MRI to exclude spinal AMV • Delivery <ul style="list-style-type: none"> – Provide prophylactic antibiotics – Avoid prolonged second-stage labor when cerebral AVM has not been excluded • Genetic counseling
TSC	<ul style="list-style-type: none"> • Rupture and hemorrhage from renal angiomyolipomas • Dyspnea from lymphangiomyomatosis • Increased risk of preeclampsia • Teratogenic effects from commonly used medications • Fetal complications: preterm delivery, fetal growth restriction, preterm premature rupture of membranes 	<p>Recommendations based on expert opinion²⁰</p> <ul style="list-style-type: none"> • Referral to nephrologist if renal dysfunction noted • Referral to pulmonologist if worsening dyspnea or multiple pneumothoraces present • Review all medications for teratogenicity • Targeted ultrasound, fetal echocardiogram for evaluation of cardiac rhabdomyoma • Consider fetal MRI • Consider increased antenatal surveillance if concern for fetal TSC • Genetic counseling
Myotonic dystrophy	<ul style="list-style-type: none"> • Abnormal uterine muscle function leading to <ul style="list-style-type: none"> – Increased risk of placenta previa, intrauterine and postpartum hemorrhage – Increased rate of cesarean deliveries and instrumental deliveries • Increased rate of preterm delivery • Higher rate of complicated urinary tract infections 	<p>Recommendations based on expert opinion^{32,36}</p> <ul style="list-style-type: none"> • Prenatal care and delivery at tertiary care center • Ultrasound to assess placental location • Consultation with anesthesiology • Regular maternal electrocardiogram screening, consider echocardiogram • Routine antenatal testing with increased surveillance if polyhydramnios is noted • Delivery

Genetic Condition	Pregnancy-Related Risks	Management Recommendations
	<ul style="list-style-type: none"> • Anesthesia complications • Fetal complications: congenital DM, polyhydramnios, decreased fetal movement 	<ul style="list-style-type: none"> – Cesarean delivery for routine obstetric indications • Genetic counseling
OTC deficiency	Increased risk for hyperammonemic episode in postpartum period	Recommendations based on expert opinion ^{46,52} <ul style="list-style-type: none"> • Baseline ammonia and plasmas amino acid levels • Referral to metabolic dietician to assure adequate oral intake • Maintenance fluids with 10% dextrose to avoid catabolism during labor and delivery • Monitor ammonia levels every 6 h during hospital course • Initiate therapy when ammonia levels are 1.5–2.0 times normal • Monitoring postpartum patients for 72 h with close follow-up as outpatient • Genetic counseling

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