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Management of Pregnancy in Women With Genetic Disorders: Part 2: Inborn Errors of Metabolism, Cystic Fibrosis, Neurofibromatosis Type 1, and Turner Syndrome in Pregnancy

Shilpa P. Chetty, MD,* Brian L. Shaffer, MD,† and Mary E. Norton, MD‡

*Fellow, ‡Professor, Department of Obstetrics and Gynecology, Stanford University School of Medicine/Lucile and Packard Children's Hospital (LPCH) at Stanford University, Stanford, CA; and †Assistant Professor, Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR

With early diagnosis and increasingly effective medical care, more women with genetic syndromes are undergoing pregnancy, often presenting challenges for providers. Each year more women with genetic disease reach childbearing age. Advances in assisted reproductive technology have enabled pregnancy in a cohort of woman who experience impaired fertility because of their underlying diagnosis. Management of these women requires health care providers from multiple specialties to provide coordinated care to optimize outcomes. Potentially, serious medical issues specific to each diagnosis may exist in the preconception, antepartum, intrapartum, and postpartum periods, all of which must be understood to allow timely diagnosis and treatment. The fetus may also face issues, both related to risk for inheritance of the genetic disorder observed in the mother as well as risks related to her chronic disease status. In this article, the second of a 2-part series, we will review the key issues for managing women with various inborn errors of metabolism during pregnancy. Additionally, we will discuss the care of women with Turner syndrome, neurofibromatosis type 1, and cystic fibrosis.

Target Audience: Obstetricians & Gynecologists and Family Physicians

Learning Objectives: After the completing the CME activity, physicians should be better able to classify the pulmonary and nutritional issues facing women with cystic fibrosis in pregnancy, assess the baseline evaluation that should take place in women with Turner syndrome, NF1 and cystic fibrosis before attempting pregnancy and evaluate the fetal risks that can be observed in women with untreated inborn errors of metabolism.

The management of pregnancy for a woman with any chronic medical condition requires a multidisciplinary approach to fully address the complex issues that arise from preconception through pregnancy and postpartum. This is especially true of women with an underlying genetic disorder, who often have medical needs that are very specific to their condition. Advances in medical care and artificial reproductive technology have allowed conception in an increasing number of women who in previous generations

The authors, faculty and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interest in, any commercial organizations pertaining to this educational activity.

Correspondence requests to: Shilpa Chetty, MD, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Stanford University, 300 Pasteur Drive, HH-333, Stanford, CA 94305. E-mail: schetty@stanford.edu.

would have been unable to reach childbearing age or have the ability to become pregnant. This cohort of women requires the coordinated care of maternal-fetal medicine physicians, geneticists, genetic counselors, anesthesiologists, and various medical subspecialists during their pregnancy. It is important to enlist the aid of those that are familiar with the patient's medical history, as many syndromes have variable expression. In the first of this 2-part series, syndromes with connective tissue, muscle, vascular, or skeletal involvement were discussed. In this article, we will review the management of several of the more common biochemical disorders as well as other conditions that require increased surveillance in pregnancy, including cystic fibrosis (CF), neurofibromatosis type 1, and Turner syndrome.

INBORN ERRORS OF METABOLISM

Most maternal-fetal medicine specialists and obstetricians will manage few women with inborn errors of metabolism (IEM) because of the relatively low incidence of these disorders. However, as early detection of IEMs and clinical management continues to improve, there now exists an increasing number of women who are of childbearing age with these diagnoses. There are a number of different IEMs, and we will explore a few of the more common disorders that have a clinically significant impact on the mother, the fetus, or both.

Urea Cycle Disorders

Urea cycle defects are a group of disorders characterized by a deficiency in one of the 6 enzymes that comprise the urea cycle. Impairment of the urea cycle results in a buildup of ammonia following protein metabolism. Hyperammonemia results in neurologic damage, coma, or death if not treated. Treatment includes protein restriction and the use of medications, such as sodium benzoate and sodium phenylbutyrate, which act as nitrogen scavengers and activate alternative pathways for nitrogen excretion. Liver transplantation is also used in the management of these patients, and it is considered curative for specific disorders, including ornithine transcarbamylase deficiency (OTC) and carbamoyl phosphate synthasedeficiency.[1]

OTC DEFICIENCY

OTC deficiency is the most common of the urea cycle defects, with an incidence of approximately 1 in 14,000. It is also the only X-linked urea cycle defect and therefore, males experience more severe clinical manifestations, although female carriers can be symptomatic to a lesser degree. Symptom onset usually occurs in the neonatal period or rarely later in infancy or childhood. The presentation can include recurrent vomiting, lethargy, cerebral edema, or coma due to hyperammonemia.

As with most X-linked disorders, female carriers of OTC deficiency are typically asymptomatic. However, because X-chromosome inactivation in women is random in each cell, either the mutant or wild-type OTC gene may be expressed in each cell throughout the body. About 15% of female carriers are symptomatic to some degree because of skewed X-inactivation or unequal lyonization. Women often remain undiagnosed because the phenotype is rare and quite variable and often include nonspecific symptoms such as migraines, recurrent vomiting, and anorexia. Many of these women avoid protein in their diet. Recognition of this disorder in women may occur following periods of physiologic stress that result in significant catabolism, and it can be provoked by protein loading, medical illness, or pregnancy, particularly the postpartum period.[2]

The management of pregnant OTC deficiency carriers has been described in numerous case reports and case series. Earlier articles often reported a grim prognosis, in some cases, due to the lack of a diagnosis at the time of pregnancy. Maestri et al discussed the clinically variable presentation of OTC deficiency carriers in a study published in 1998. They identified 79 women as carriers of a mutant OTC allele and compared them with 96 controls with no OTC mutation and did not identify any significant differences in obstetric history between these groups.[3]

Mendez-Figueroa et al provide a thorough management plan for pregnant women with OTC deficiency. During the antenatal course, baseline plasma amino acids and serum ammonia levels should be obtained in addition to routine prenatal laboratories. Patients should be followed by a nutritionist who can help to meet nutritional goals. Management may include supplementation of deficient amino acids (e.g., arginine and citrulline) and adherence to a protein-restricted diet.[4] Women with OTC deficiency who develop gestational diabetes, in particular, require careful consultation regarding dietary management, which can be complex. Patients may develop tonic-clonic seizures if hyperammonemia occurs, and this must be differentiated from eclampsia.

The impact of OTC deficiency on the fetus and fetal well-being is not well documented. Mendez-

Figueroa et al describe antepartum surveillance starting at 32 weeks with biophysical profile testing.[4] With regard to delivery planning, affected women may benefit from induction of labor to ensure that the multiple providers can best execute the plan of care. The intrapartum period represents a time of high metabolic stress, and therefore poses a risk for the development of hyperammonemia. To avoid periods of prolonged fasting and a catabolic state, it is advised that patients receive continuous dextrose (e.g., D10) infusion throughout labor. If blood glucose levels are consistently elevated, IV insulin may be administered to aid in achieving a euglycemic state. Patients who undergo planned cesarean delivery should be admitted on the night before the procedure to receive dextrose infusion during the fasting period. Plasma ammonia levels should be evaluated at regular intervals during the intrapartum and postpartum period. If an elevation is noted, the patient may benefit from treatment with ammonia scavenging agents such as sodium benzoate to prevent hyperammonemic complications. In the postpartum period, close observation for a prolonged period is warranted, as high metabolic demands can precipitate complications. Dietary restrictions, frequent laboratory ammonia evaluations, and monitoring of symptoms are critical. Ideally, metabolic geneticists should be involved in the antepartum, intrapartum, and postpartum management of these patients.[3,4,5]

In known OTC deficiency carriers who become pregnant or plan to become pregnant, confirmation of the causative OTC mutation should be performed. Genetic counseling is recommended regarding disease manifestations in pregnancy and the X-linked inheritance, which results in a 50% chance of disease transmission to male offspring. Females are also at a 50% risk of inheriting the abnormal allele from carrier mothers and should therefore be evaluated by a metabolic geneticist in the neonatal period. Prenatal diagnosis is possible in the setting of a known OTC mutation with preimplantation genetic diagnosis, chorionic villus sampling (CVS), or amniocentesis. Prenatal diagnosis is helpful to allow involvement of the neonatology team at birth and prevents the development of hyperammonemia and ensuing complications in the newborn period.[4]

Amino Acid Disorders

Amino acid disorders are characterized by impaired synthesis and degradation of various amino acids. The manifestations typically are noted in infancy; therefore, newborn screening now results in the detection of many such disorders.

PHENYLKETONURIA

Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficient activity of the enzyme phenylalanine hydroxylase (PAH). The prevalence of *PAH* gene mutations varies greatly by ethnicity and is most common in individuals of Northern European descent, with an incidence of 1 in 10,000. Hydroxylation of phenylalanine to tyrosine cannot occur without adequate PAH enzyme activity, and affected persons are intolerant of the dietary intake of the essential amino acid phenylalanine. Accumulation of phenylalanine and its metabolites is neurotoxic and if left untreated, it can lead to progressive mental retardation. Disease manifestations in infancy include vomiting, irritability, lethargy, and increased tone. A characteristic "mousy" odor of the urine has been described in affected individuals. This odor is attributed to an increase in the phenylalanine metabolite—phenyl acetic acid. If untreated, phenylalanine levels may reach 20 times normal; such elevated phenylalanine can result in multiple manifestations, including decreased skin and hair pigmentation, due to associated inhibition of tyrosinase. Neurologic deficits result from decreased myelin formation and decreased production of various neurotransmitters. The disease severity varies with compliance with treatment as well as with the specific PAH genotype.[6]

The introduction of newborn screening in the United States has been very effective in diagnosing PKU within the first week of life, before development of irreversible neurologic impairment. The goal of treatment is to maintain plasma phenylalanine concentrations of 120 to 360 μmol/L (2–6 mg/dL) by adherence to a phenylalanine restricted, low protein diet supplemented with a phenylalanine-free medical formula. Adequate compliance with a treatment regimen started before 3 months of age can result in minimal to no manifestations.[6] Although historically children were allowed to discontinue the strict dietary regimen at age 6, it is now recommended that dietary restriction be lifelong, as neurocognitive decline and behavioral abnormalities occur even in later childhood and adulthood with prolonged exposure to high phenylalanine levels.

Women with PKU who are considering pregnancy should be counseled regarding the importance of treatment compliance in the preconception period and throughout pregnancy. Treatment goals include plasma phenylalanine concentrations between 120

and 360 μmol/L (2–6 mg/dL) for at least 3 months before conception. During pregnancy, women should be followed closely by a nutritionist as protein and dietary phenylalanine requirements will change with gestational age. Diet should be optimized to allow for adequate weight gain during pregnancy.[7]

Women with untreated PKU during conception and the first trimester are at increased risk to have a fetus with multiple abnormalities due to the teratogenic effects of hyperphenylalaninemia. The most commonly observed anomalies include congenital heart disease, microcephaly, intrauterine growth restriction, and neurodevelopmental disability. Platt et al evaluated pregnancy outcomes in 576 women with hyperphenylalaninemia during a 12-year-period as part of the Maternal Phenylketonuria Collaborative Study. The outcomes were classified according to the phenotype of hyperphenylalaninemia and the gestational age at the time that treatment was started. The target phenylalanine level in the latter part of this study was 120 to 360 μmol/L (2–6 mg/dL). This long-term study demonstrated that phenylalanine restricted diet before conception or by 8 to 10 weeks gestation significantly decreased the incidence of congenital heart disease and microcephaly in offspring of affected mothers. Maternal phenylalanine levels >900 μmol/L were associated with an 85% risk for microcephaly and 26% risk for growth restriction. Intellectual development of the offspring was optimal if maternal diet restriction began in the preconception period.[8]

Tetrahydrobiopterin is a naturally occurring essential cofactor of PAH and is used in the degradation of phenylalanine. Sapropterin is a synthetic preparation of tetrahydrobiopterin that is currently used to treat PKU in responsive individuals. If pregnant women are unable to maintain the recommended treatment guidelines to achieve target phenylalanine levels and have been shown to be responsive to sapropterin, consideration of its use should be considered as it may assist in reaching phenylalanine targets. Currently, there is a registry available for all women who take this medication in pregnancy, and participation should be strongly encouraged.

Long-term neurodevelopmental outcomes in children born to mothers with PKU were investigated by Waisbran et al in a follow-up to the Maternal PKU Collaborative Study. Their findings supported optimal dietary control as being associated with improved intellectual development. These investigators also found that children born to women with PKU had worse performance on developmental testing at age 4 years than at age 2 years when compared with controls, suggesting cognitive decline over time. However, long-term studies have not been performed to validate this finding.[9]

Women with PKU should undergo serial ultrasound evaluations in pregnancy because of the high incidence of growth anomalies. It is reasonable to consider performing a fetal echocardiogram due to the risk of congenital heart disease in this patient population.[8] There have been no studies that indicate any effect of PKU on the labor and delivery process.

Genetic counseling is strongly advised in women affected with PKU not only to discuss the importance of compliance with dietary restriction in the preconception period but also for discussion of prenatal testing options. The chance that her offspring will also have PKU depends on the carrier status of her partner, which varies with ethnicity although the carrier frequency is generally quite low. Partners of carriers can undergo molecular carrier testing, although without a family history, such testing is less accurate. CVS or amniocentesis can be performed for prenatal diagnosis if underlying mutations have been identified in both parents.[6]

HOMOCYSTINURIA

Homocystinuria is an autosomal recessive disorder caused by a deficiency in the enzyme cystathionine B-synthase (CBS), resulting from a mutation in the *CBS* gene. It is characterized by variable degrees of developmental delay, ectopia lentis, skeletal abnormalities, and thromboembolism. Patients may be misdiagnosed with Marfan syndrome as there are shared characteristics, specifically the marfanoid body habitus, ectopia lentis, and arachnodactyly. Patients are typically characterized as having B_6-responsive homocystinuria or B_6-nonresponsive homocystinuria, with B_6 responsive patients exhibiting milder manifestations. The goal of therapy is to prevent secondary complications by maintaining normal plasma homocysteine concentrations using protein and methionine-restricted diets as well as supplementation with betaine, folic acid, and vitamin B_{12}.[10] Although developmental delay is observed in some affected persons, many patients have normal intelligence. Early diagnosis with newborn screening allows earlier treatment and can avert neurologic decline in both B_6 responsive and nonresponsive patients.[11]

There is no evidence that women with homocystinuria have impaired fertility. Unlike PKU, elevated homocysteine levels do not appear to have teratogenic effects. Levy et al described the pregnancy

outcomes of 11 women with homocystinuria and their 15 pregnancies. In this group, there were 5 B_6 responsive and 6 nonresponsive patients, and they found no increase in adverse obstetric or neonatal outcomes.[11] Pierre et al and others have reported the use of betaine in affected women throughout pregnancy to decrease hyperhomocysteinemia and to improve hypomethioninemia, with no adverse maternal or fetal effects.[12–14]

The primary concern in women with homocystinuria during pregnancy is the increased risk for thromboembolism in the puerperium. In an observational study by Levy et al, only 5 of the 11 women were treated with anticoagulation; 1 woman developed a superficial venous thromboembolism. The potential benefits of anticoagulation far outweigh the risk of thromboembolism in this high-risk population, therefore, prophylactic anticoagulation is recommended in the third trimester and postpartum periods.[11]

Genetic counseling is indicated for women with homocystinuria to discuss risk to her offspring. Risk of an affected woman having an affected fetus depends on the carrier status of her partner, which is dependent on ethnicity. Prenatal testing can be performed by CVS and amniocentesis if the fetus is at risk and the disease-causing mutations are known. CBS enzyme activity can also be used for diagnosis with cultured amniocytes but not chorionic villi, which have low CBS enzyme activity even in unaffected individuals. Measurement of total homocysteine in cell-free amniotic fluid is also possible to aid in diagnosis.[10]

Organic Acid Disorders

Organic acid disorders are a group of metabolic diseases that result from deficiencies in the enzymes responsible for the breakdown of branched-chain amino acids or lysine. Such enzyme deficiencies result in an accumulation of non–amino organic acids in urine. Severe forms of these disorders are characterized by recurrent episodes of metabolic acidosis and hyperammonemia if left untreated. Treatment typically consists of protein restriction and carnitine supplementation.

MAPLE SYRUP URINE DISEASE

Maple syrup urine disease (MSUD) is an organic acidemia that results from a defect in the enzyme responsible for metabolizing the branched chain amino acids leucine, isoleucine, and valine. The disorder is transmitted in an autosomal recessive manner, and there have been 3 genes identified as responsible for various subtypes: *BCKDHA*, *BCKDHB*, and *DBT*. The disorder is relatively rare with a reported incidence of approximately 1:185,000 live births. Some groups, specifically the Mennonite population, have an incidence as high as 1:175. The enzyme defect results in accumulation of leucine, isoleucine, and valine, which if left untreated, can cause neurologic impairment. The name of the disorder is derived from the characteristic odor of cerumen and urine in those affected. The disease symptoms are typically noted during the first week of life when infants are found to have poor feeding, emesis, lethargy, abnormal tone, and finally coma. Disease severity is associated with the level of enzyme activity in the affected individual. Newborn screening has allowed for early detection of MSUD and, therefore, prevention of early neurologic insult. Improved long-term outcomes with treatment and dietary intervention.[15]

Treatment of MSUD includes leucine restriction, use of specific feeding formulas that do not contain branched chain amino acids, and supplementation of isoleucine and valine. Metabolic crisis can occur in the setting of increased stress due to illness. The goal of treatment is to keep metabolite levels below pathogenic concentrations.[15]

Maternal MSUD is more common since the implementation of newborn screening, which has allowed early diagnosis of the disorder and prevention of neurologic sequelae associated with untreated crises.[2] Unlike with PKU, there have not been studies regarding the teratogenic effects of elevated branched chain amino acids. However, these do cross the placenta and have given the adverse impact in newborns, there is concern that elevated levels could be teratogenic. Case reports of successful pregnancy management have been described in the literature by both Van Calcar et al and Grunewald et al. They recommend rigorous dietary control before conception and throughout pregnancy. Maternal nutritional status must be monitored carefully, and adequate protein and calories must be delivered to allow appropriate fetal growth. In the cases described in the literature, women were able to deliver at 36 to 40 weeks and were not observed to be at increased risk for obstetric complications, except those related to fetal growth. In both reports, however, the postpartum period was found to be a vulnerable time for maternal metabolic crisis due to the stress induced by labor and the various tissue catabolic processes.[16,17]

Offspring of women with MSUD are obligate heterozygotes and typically asymptomatic. If there is

concern for an affected fetus (e.g., parental consanguinity), prenatal diagnosis is possible with amniocentesis or CVS, if the disease-causing mutation has been identified.[15]

FATTY ACID OXIDATION DISORDERS

Fatty acid oxidation (FAO) disorders are a group of autosomal recessive disorders characterized by deficiency in various enzymes necessary for the conversion of fats to energy. Mitochondrial FAO fuels hepatic ketogenesis and restores hepatic glycogen stores used during periods of prolonged fasting. If the ability to restore energy stores is compromised, affected individuals may experience hypoketotic hypoglycemia, liver dysfunction, cardiomyopathy, lethargy, and coma when faced with fasting or stress.[2,18]

The fatty oxidation pathway includes multiple enzymes, including short-, medium-, long- and very long chain acyl-CoA dehydrogenase, and carnitine palmitoyltransferase IA and II.

Medium chain acyl-CoA dehydrogenase deficiency (MCAD) is the most common of the FAO disorders, with an incidence ranging between 1:4900 and 1:17,000. It is most prevalent among whites and northern Europeans. The onset of symptoms is typically between 3 and 24 months of age, but may present later, even into adulthood. Once the diagnosis of MCAD has been made, instituting frequent feedings can prevent metabolic decompensation. Untreated individuals with MCAD are at increased risk for death during their first metabolic crisis, and MCAD is thought to be responsible for approximately 5% of sudden infant death cases.[18]

The impact of FAO disorders on pregnancy is primarily related to women who have affected fetuses rather those with maternal FAO deficiency. Maternal liver disease, particularly acute fatty liver, has been associated with pregnancies in which the fetus is affected with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). Several authors have demonstrated that short- and medium-chain defects can be implicated in maternal liver disease during pregnancy as well.[19,20] Browning et al demonstrated an 18.1-fold increase in maternal liver disease in pregnancies complicated by any fetal fatty oxidation disorder when compared with controls with unaffected fetuses.[19] In a prospective analysis by Ibdah et al, authors found that 15% to 20% of pregnancies complicated by acute fatty liver of pregnancy (AFLP), and 2% of pregnancies with hemolysis, elevated liver enzymes, and low platelet count (HELLP) are associated with fetal LCHAD deficiency.[21,22] Ibdah et al and others have explored the molecular basis for this association and hypothesized that the accumulation of 3-hydroxy-fatty acids may be a maternal hepatotoxin. The obligate heterozygote status of the mother may also cause reduced capacity to metabolize long-chain fatty acids particularly when faced with the increased fetal contribution.[21] Due to this association, testing for fatty oxidation disorders in the infant is recommended in the setting of maternal acute fatty liver.

The complications associated with maternal FAO disorders have not been well documented. One case of acute liver failure in the setting of undiagnosed maternal MCAD deficiency has been described.[23] This complication can occur in other individuals with undiagnosed FAO disorders under times of stress or prolonged fasting. Avoidance of prolonged fasting in affected patients during pregnancy is recommended to minimize the complications of FAO deficiency. Adequate glucose administration should be ensured during labor and the postpartum period to prevent known complications of this disease during these times of increased metabolic stress.

All known FAO disorders have an autosomal recessive inheritance pattern. The carrier frequency can be as high as 1 in 40 in the white population for MCAD deficiency; therefore, a woman with FAO deficiency and her untested, nonconsanguineous partner would have a 1/80 chance to have an affected child in each pregnancy. Prenatal diagnosis should be considered in cases in which the mother has had a previously affected child and is therefore an obligate heterozygote. As an affected fetus increases the risk of significant maternal liver disease in pregnancy, a diagnosis is helpful to provide optimal obstetric care. Molecular analysis of fetal DNA obtained by CVS or amniocentesis is possible if the disease-causing mutation has been identified. If the mutation has not been identified, biochemical analysis is possible with an assay of FAO enzymatic activity in CVS or amniocyte cultures.[18,24]

GAUCHER DISEASE

Gaucher disease (GD) is an autosomal recessive disorder that results from a mutation in the glucosidase, beta, acid gene. It is the most prevalent lysosomal storage disorder and affects approximately 1/450 Ashkenazi Jews and 1/40,000 to 1/100,000 other individuals. A deficiency in the enzyme glucocerebrosidase results in the abnormal accumulation of a complex lipid, glucocerebroside in the lysosomes of various organ systems. GD is a clinically

heterogeneous disorder with interfamilial variable expressivity. Gross enlargement of the liver and spleen occurs as a result of glucocerebroside accumulation in the reticuloendothelial system. Deposition of glucocerebroside in the bone marrow causes decreased erythrocyte and platelet production. Bone lesions result in pain, osteonecrosis, and associated complications.

GD is classified into 5 different types based on the primary manifestation and age of onset. Those most commonly seen in adults are type 1, type 3, and the cardiovascular form; therefore, these are mostly likely to be encountered in pregnant women. Type 1 GD manifests with bone disease, hepatosplenomegaly, bone marrow dysfunction, pulmonary manifestations, and sparing of the central nervous system (CNS). Type 3 GD is distinguished by the onset of primary neurologic disease with oculomotor apraxia; progressive myoclonic epilepsy; and hepatomegaly, splenomegaly, cytopenia, and pulmonary disease. The cardiovascular subtype is characterized by oculomotor apraxia, calcification of the mitral and aortic valves, corneal opacity, and mild splenomegaly.[25]

GD has not been demonstrated to decrease fertility. Contraindications to pregnancy are related to the associated disease manifestations, including severe pulmonary disease, pulmonary hypertension, or cardiovascular disease. If these contraindications are not present, pregnancy in a woman with GD is generally well tolerated, although should involve careful coordination by multiple providers who are familiar with this disease.[26]

In a woman with GD and who is considering pregnancy, a review of her baseline disease state and medications should be performed. Many patients with GD are treated with an enzyme inhibitor—known as miglustat—to reduce the manifestations in the liver, spleen, or bones; it is recommended that this medication be discontinued for at least 3 months before pregnancy. Miglustat is classified as pregnancy category X due to animal studies demonstrating decreased live birth rate and decreased birth weight of rat pups following maternal exposure during the periods of preconception and organogenesis. Bisphosphonates are also used in the treatment of the skeletal manifestations of GD. Exposure is associated with potential fetal risks as it crosses the placenta and may theoretically result in hypocalcemia in the fetus. However, many cases of in utero exposure have been reported with no adverse fetal effects, therefore, the clinical necessity must be assessed for each patient.[26–28]

Women who are receiving enzyme replacement therapy, such as alglucerase or imiglucerase, should continue such therapy, as discontinuation has been associated with worse outcomes. Zimran et al report that women who were treated with enzyme replacement therapy had decreased complications related to bleeding in the intrapartum and postpartum period compared with an untreated group of GD patients. No adverse fetal outcomes were reported in the group of patients who had used enzyme replacement in the first trimester.[28]

The nutritional status of GD patients should be assessed and optimized prenatally.

Supplementation of vitamin B_{12}, vitamin D, and folic acid are typically necessary in affected women and should be recommended both before and during pregnancy. Levels should be evaluated in the second and third trimesters and optimized as necessary. Iron status should be followed, as significant anemia can occur in pregnant women with GD. This is most reliably assessed by serum iron levels and percentage transferrin receptor saturation, as ferritin levels may be high despite low iron levels in affected patients. Additionally, calcium supplementation is important preconception and during pregnancy, as pregnancy may deplete calcium stores and result in advancing osteoporosis.

In patients who have undergone splenectomy, there is an increased risk of infection; therefore, these women should be encouraged to complete all immunizations before pregnancy.[26]

In terms of managing GD in pregnancy, there are multiple considerations. The underlying bone disease and hematologic issues often worsen during the course of pregnancy. Bone pain should be treated with pain medication as needed, and MRI used if indicated to evaluate any suspicion of infection or necrosis. If there is significant bone disease or in the presence of prosthetic joints before pregnancy, consultation with orthopedic surgery is advised.[26] There have been some reports documenting increasing visceromegaly during pregnancy in those affected with GD. Ultrasound evaluation of the liver and spleen may be helpful if this is occurs.

Evaluation of blood count, platelet function, and coagulation studies should be performed in each trimester and should be closed at the time of delivery. The incidence of postpartum hemorrhage is increased in these patients, thought to be related specifically to thrombocytopenia and platelet dysfunction. Platelet dysfunction has been treated with desmopressin, which induces platelet degranulation.[29] Coordination of care with a hematologist is recommended for

patients who exhibit such hematologic abnormalities. In addition, consultation with anesthesia is recommended before delivery to discuss options and limitations for regional anesthesia, which will be influenced by the diagnosis of thrombocytopenia or other coagulopathy.

Despite the multiple manifestations of GD, there are limited data indicating adverse fetal effects specifically due to GD. If the affected woman has underlying cardiac or pulmonary manifestations, these can present an increased risk of decreased fetal growth and need for fetal assessment in the third trimester.[26]

Patients with GD planning a pregnancy should have genetic counseling. GD is an autosomal recessive disorder, and the carrier frequency is significant in certain populations such as Ashkenazi Jews, in whom the carrier rate is 1 in 18. Therefore, an affected woman with an untested Ashkenazi Jewish partner would have a risk of 1/36 of having an affected child. Prenatal diagnosis is available for pregnancies at increased risk. If the underlying disease-causing mutation is known, fetal DNA obtained by invasive methods can be tested by mutation analysis. If the mutation has not been identified in affected family members, analysis of glucosylceramidase enzymatic activity of fetal cells obtained by CVS or amniocentesis can be performed.[25]

NEUROFIBROMATOSIS 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder, with an incidence of approximately 1:3000; approximately 50% of cases are familial, whereas 50% occur as new mutations. The disorder is characterized by the presence of pigmented lesions in the form of café-au-lait macules, axillary and inguinal freckling, cutaneous neurofibromas, lisch nodules of the iris, and osseus lesions. Tumors of the spinal cord or cranial nerves can be observed and have the potential for malignant transformation. Mutations in the gene for NFI, located on chromosome 17, are implicated in the majority of those affected with NF1. A large degree of variable expressivity, even within a family, can be observed in those affected.[30]

The incidence of NF1 in pregnancy is similar to that of the general population, ranging from approximately 1:3000 to 5000. There does not appear to be a decrease in fertility in affected women. Dugoff and Sujansky reported on the pregnancy outcomes of 105 women with neurofibromatosis and their 247 pregnancies. In terms of the effect of pregnancy on NF1, the most consistent finding was an increase in growth of new or existing neurofibromas observed in 55% to 60% of women. About 30% of these women observed a decrease in neurofibroma size in the postpartum period, suggesting a hormonal influence on neurofibroma development.[31,32]

In terms of the effect of NF1 on pregnancy, some reports have suggested an increase in obstetric complications.[32] In the study by Dugoff and Sujasky, which comprises the largest reported series, women with NF1 did not experience an increased incidence of hypertensive disorders of pregnancy, growth restriction, preterm delivery, or overall perinatal mortality. They did demonstrate an increased rate (36%) of cesarean delivery, which appears to be higher than the general population. Approximately 55% of these cesarean deliveries were due to cephalopelvic disproportion or fetal malpresentation; this was postulated by the authors to be related to undiagnosed pelvic neurofibromas or kyphoscoliosis of the lower spine.[31]

Recent case reports have documented complications related to aggressive malignant tumors diagnosed in the antepartum period in affected women. Nelson et al described a case of a mediastinal malignant peripheral nerve sheath tumor in a woman diagnosed at 23 weeks' gestation, which ultimately resulted in death.[32] Others have also reported malignancies, highlighting the point that patients with NF1 have an increased risk of malignancy and should be monitored closely for masses that behave differently from other neurofibromatous growths.[33] Surveillance during pregnancy is best achieved with MRI.

Although an increased incidence of obstetric complications is not reported in all series, it is reasonable to monitor women with NF1 closely for both maternal and fetal well-being. Women with neurofibromatosis should be assessed at their first visit for any history of seizures or visual disturbance. If kyphoscoliosis is noted, pulmonary function tests should be performed to assess lung function. Because growth of neurofibromas is common during pregnancy, the status of large lesions, particularly those in the pelvic area, should be monitored. Ultrasound assessment of fetal growth is recommended, particularly in those with pregnancies complicated by hypertension. Antepartum consultation with anesthesiology is recommended due to frequent kyphoscoliosis and potential challenges for regional anesthesia.[32–34]

Women with NF1 should undergo genetic counseling as each pregnancy carries a 50% recurrence risk. Complete penetrance is noted in affected individuals, but clinical manifestations can vary greatly even within a family. If prenatal diagnosis is desired, the

disease-causing mutation must be identified. CVS or amniocentesis can then be performed to obtain fetal DNA for mutation analysis. Ultrasound diagnosis of NF1 has been reported but is not reliable as disease manifestations can vary greatly in terms of both onset and severity.[35]

TURNER SYNDROME

Turner syndrome affects approximately 1 in 2500 live-born females and results from complete or partial absence of the second X chromosome, with or without mosaicism. Characteristic phenotypic features include edema of the hands, feet, or nuchal fold, left-sided cardiac anomalies, cubitus valgus, low set ears, low hairline, high arched palate, or chronic otitis media. A diagnosis of Turner syndrome should also be considered in females who have delayed puberty, primary infertility, and/or growth failure, especially if any of the above phenotypic findings are present.

Prenatal diagnosis and early identification of patients with Turner syndrome have allowed improved clinical care, and many of these individuals have been followed from early ages by geneticists and endocrinologists. Although pubertal development has been observed to occur spontaneously in a small percentage of Turner syndrome patients, approximately 90% have ovarian dysgenesis and gonadal failure. The use of estrogen therapy allows breast and uterine development; this treatment is most often coordinated under the care of a pediatric endocrinologist.[36]

Because of the high incidence of gonadal failure, few patients have spontaneous pregnancies. However, assisted reproduction has resulted in successful pregnancies in women with Turner syndrome, and recent studies have shown that pregnancy rates are similar to other women who undergo infertility treatments.

With greater use of assisted reproductive technology (ART) in women with TS, it has been recognized that these women face a substantial risk of maternal complications, including a high rate of maternal mortality. Such complications include an increased risk of pregnancy-induced hypertensive disorders as well as acute cardiovascular issues, such as aortic dilatation and dissection.[37] Because of these potential complications, women with Turner syndrome should undergo a comprehensive cardiac evaluation before assisted reproduction or conception.[38,39] It has been suggested that contraindications to pregnancy include previous aortic coarctation or dissection and aortic size >25 mm/m^2, although aortic dissection in pregnancy has been reported in TS women with a normal aortic root.[40] Finally, exclusive single embryo transfer is preferred in women with TS who do decide to proceed with oocyte donation, given the increased medical risks associated with multiple gestations. If pregnancy is attempted in the presence of a cardiac anomaly, careful coordination with perinatology and cardiology should take place in the antepartum period.

From an endocrine standpoint, women with Turner syndrome have an increased risk of diabetes and thyroid dysfunction, and they should be tested and monitored for these conditions during pregnancy. Short stature is a consistent feature in women with Turner syndrome secondary to haploinsufficiency of short-stature homeobox-containing gene, resulting in adult stature approximately 20 cm less than the average female adult height.[41,42] Short stature and cephalopelvic disproportion have been implicated in the increased cesarean delivery rate in patients with Turner syndrome. In a case series by Hadnott et al, 13 pregnancies were observed in a cohort of 276 patients with Turner syndrome. Of these 13 pregnancies, 10 were delivered via cesarean delivery, most due to cephalopelvic disproportion. Similar issues have been observed in a number of other reports.[43]

Fetal complications in women with Turner syndrome have been reported to include an increased rate of spontaneous abortion, fetal malformation, and chromosomal anomalies.[44] In the report by Hadnott et al, of pregnancy outcomes in 13 pregnancies to TS women, none of the infants had chromosomal anomalies. In the 6 who were conceived with ART, 3 resulted in infants with low birth weight.[43] Georgopoulos et al also report growth restriction in an infant born to a woman with Turner syndrome who underwent ART. Growth restriction may be primarily related to the ART or the underlying maternal cardiovascular issues; therefore, increased frequency of prenatal ultrasounds to monitor for growth is warranted.[45]

Genetic counseling can be of benefit for a woman with Turner Syndrome. The maternal outcome of pregnancy in women with Turner syndrome is predominantly dictated by the underlying cardiovascular status before conception. There may be an increased chance of transmission of an abnormal chromosome to offspring if the woman with TS has an abnormal X chromosome. Because the number of reported pregnancies is relatively low, the precise risk of transmission to offspring is unknown.

CYSTIC FIBROSIS

CF is an autosomal recessive disorder that results from mutations in the CF transmembrane conductance regulator (CFTR) gene. The presence of 2 disease-causing mutations in CFTR results in dysfunction of the CFTR located on epithelial cell membranes. Epithelial cell function is compromised in multiple organs, including the respiratory tract, exocrine pancreas, sweat glands, intestine, and hepatobiliary systems, leading to the multiple manifestations observed in CF. The major cause of morbidity in CF patients is due to pulmonary disease; chronic inflammation related to recurrent sinopulmonary infections results in damage to airways and lung parenchyma. Bronchiectasis, abscesses, and cysts are observed in affected patients, contributing to the eventual development of respiratory failure in many patients. Insufficient exocrine pancreatic function produces intestinal malabsorption, and patients exhibit overall compromised nutritional status with loss of fat-soluble vitamins and zinc. Pancreatic fibrosis and decreased islet cells contribute to the development of CF-related diabetes mellitus (CFRD), observed with increasing incidence in adult patients with CF. Meconium ileus is observed in approximately 20% of newborns.[46]

Improvements in managing the chronic medical issues that CF patients face has resulted in an increasing number of those affected reaching adulthood, with the median survival reaching 37.4 years of age in 2008. As such, the issues facing a woman with CF in pregnancy have been explored in depth in the medical literature.[47] Women with CF experience delayed puberty and menarche related to their chronic disease state and poor nutritional status and growth from intestinal malabsorption. Although some women with CF experience infertility thought to be related to abnormal cervical mucus and anovulatory cycles, most of them (aged 13 to 45 years) are fertile, with the rate of live births reported at 1.9 per 100.[48]

The management of pregnancy in a woman with CF requires a multidisciplinary approach. If a woman is examined in the preconception period, it is important to optimize the overall nutritional status, as well as baseline pulmonary and cardiac function.

Women with CF are typically managed with a variety of medications, including oral antibiotics, mucolytics, and often pancreatic enzyme replacement therapy. Antibiotic use should be reviewed to ensure that none with teratogenic potential is used. Mucolytics, such as recombinant human DNase and hypertonic saline, are commonly used in CF patients. McMullen et al reviewed data from the Epidemiologic Study of Cystic Fibrosis (ESCF) and found that of 24,000 individuals with CF in the United States and Canada, there were 216 pregnancies. Approximately 39% of these women used dornase alpha, or recombinant alpha DNase, during pregnancy. No adverse outcomes were reported by these authors, although this was not the objective of the article. Drug studies conducted in nonhuman primates have not shown transmission to the fetus or into amniotic fluid after IV administration. Pancreatic enzyme replacement therapy has not been shown to cause any significant risk during pregnancy and is very instrumental in patients with CF who experience malabsorption due to pancreatic insufficiency.[48,49]

Malabsorption from pancreatic insufficiency is implicated in the poor nutritional status that women with CF often exhibit. Ideally, women should receive sufficient vitamin supplementation in the preconception period to aid in their overall nutritional status in pregnancy. Despite this, the increased resting energy expenditure, in addition to malnutrition, results in challenges in weight gain during pregnancy. Increased risk of preterm delivery and poor fetal growth is associated with low body mass index in pregnancy; therefore, close observation of caloric intake and maternal weight gain is advisable. If possible, women with CF should be at least 90% of ideal body weight before conception. Patients with CF are susceptible to CFRD with increasing age and therefore, women should be screened early in pregnancy for gestational diabetes if they do not already have a diagnosis of CFRD before conception. Balancing the competing issues of increasing maternal weight gain while managing CFRD is complex, and using the aid of a nutritionist familiar with CF is critical.[47]

The pulmonary issues facing women with CF are significant and may be complicated further due to pregnancy. There have been a number of conflicting studies reporting the influence of pregnancy on underlying lung function and the affect of compromised lung function on pregnancy. The consensus of multiple studies seems to indicate that women with mild-to-moderate pulmonary disease, typically defined as forced expiratory volume in 1 second (FEV1) $>60\%$, are not associated with increased maternal morbidity during pregnancy. Severe lung disease, with pulmonary hypertension or cor pulmonale, is associated with increased incidence of adverse maternal outcomes. There has not been a strict FEV1 value under which pregnancy is contraindicated, but the baseline pulmonary function should be taken into consideration together with other aspects of the patient's clinical status. Pregnancy has not been consistently implicated in accelerated decline in lung function

in patients with CF. Baseline evaluation of pulmonary status is warranted and should include a chest radiograph, pulmonary function tests, arterial blood gases, and sputum cultures. Coordination of care with pulmonology is advised to enhance outcomes for patients with CF. Patients should undergo serial PFTs during pregnancy as indicated by the patient's baseline pulmonary status.[50,51]

In terms of fetal outcome, preterm labor has been reported in approximately 25% of pregnant CF patients. This may be related to poor nutritional status and decreased weight gain in the mother. Severely compromised maternal lung function can lead to iatrogenic prematurity if preterm delivery is necessary for maternal health. Frequent assessment of fetal growth should be performed in addition to fetal surveillance in the third trimester.[47,50,52,53]

Limitations of the labor and delivery process will likely be determined by the underlying pulmonary function in the patient with CF. Consultation with anesthesiology before labor is advisable since the patient may have underlying pulmonary or cardiac dysfunction. Cesarean delivery is not recommended unless necessary for obstetric indications.[51,54]

Affected women in the preconception period should undergo genetic counseling. Offspring of women with CF are obligate heterozygotes. Because of the high carrier frequency in certain populations, 1 in 25 in whites, there is a considerable likelihood for heterozygous status in the partner, increasing the chance of having an affected infant. Determining carrier status of the partner may be more challenging depending on ethnicity, as there is variation in sensitivity of the available genetic screening tests. Women should be aware that although negative screening tests in a partner decrease the risk of having an affected child, some residual risk remains because of limitations of current mutation testing.[46]

SUMMARY

Increasing numbers of women with inherited genetic disorders are now surviving to adulthood and pursuing pregnancy, either spontaneously or through assisted reproduction. Women with chronic medical conditions and those with complex syndromes frequently benefit from an integrated, multidisciplinary approach to management. In many cases, relatively few pregnancies have been reported with a given condition, and there are few data available on which to base management decisions. Many women will have been cared for by a geneticist and other subspecialists, including these providers in management decisions will take advantage of their experience with a given patient's disease process and history. A thoughtful approach to labor and delivery, including antenatal consultation with anesthesiology, is often of benefit. In some cases, a given disorder may be associated with a high maternal and perinatal morbidity and mortality rate, and for some women adoption or surrogacy may be the best option for pursuing a family. Preconception consultation is of particular value for women with genetic disorders and should be encouraged by providers as these patients reach reproductive age and begin to consider pregnancy.

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