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7

Obstetric care in women with genetic disorders

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The management of pregnant women who are themselves affected with genetic diseases is an increasingly relevant and important issue. Improvements in early diagnosis and management of genetic disease, as well as advances in assisted reproductive technology have impacted pregnancy rates in a cohort of women who may not have otherwise been able to conceive. A multidisciplinary approach is key to the management of pregnant women with complex health conditions, including genetic diseases. Pertinent issues should be addressed in the preconception, antepartum, intrapartum and postpartum periods to optimize maternal and fetal health. Additionally, counseling regarding risk of inheritance in offspring and options for prenatal diagnosis should be reviewed if available. This reviews aims to help provide background and insight into the management strategies for various commonly encountered and complex genetic conditions in the setting of pregnancy

Metabolic disorders

Inborn errors of metabolism are rare disorders that result from accumulation or deficiency of a metabolite due to abnormal function or absence of key enzymes. Early diagnosis and treatment are imperative for improved outcomes. Phenylketonuria and fatty oxidation disorders are reviewed in this paper due to unique associated fetal and obstetric issues.

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Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficient activity of the enzyme phenylalanine hydroxylase (PAH), leading to an inability to tolerate intake of the essential amino acid, phenylalanine. Pregnancy in women with PKU is increasingly common due in part to early diagnosis via newborn screening, allowing adequate treatment and better outcomes. PAH gene mutations, and therefore PKU, are most common in individuals of Northern European descent, in which the disorder has an incidence of 1 in 10,000.

Adequate PAH enzyme activity is necessary for phenylalanine metabolism. Ingestion of dietary phenylalanine in affected individuals leads to accumulation of phenylalanine and its metabolites. Such metabolites are neurotoxic, and if left untreated, can lead to microcephaly, epilepsy and progressive intellectual disability. Disease manifestations in infancy include vomiting, irritability, lethargy, and increased tone. A characteristic musty odor of the urine in those affected has been described and is attributed to an increase in phenyl acetic acid, one of the phenylalanine metabolites. If untreated, phenylalanine levels may reach 20 times normal; such elevated phenylalanine can result in additional 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 [1–3].

The introduction of newborn screening in the United States has been very effective in diagnosing PKU in infants within the first week of life and instituting treatment prior to development of irreversible neurologic impairment. The goal of treatment is to maintain plasma phenylalanine concentrations of 120-360 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 prior to 3 months of age can result in minimal to no manifestations of PKU [3]. Although diet modification is the mainstay of treatment, FDA approval of Sapropterin allows an additional treatment option. Sapropterin reduces blood Phe levels in patients with hyperphenylalaninemia (HPA) due to BH_4-responsive PKU. Lifelong medical management is recommended, as neurocognitive decline and behavior abnormalities will occur even in later childhood and adulthood with prolonged exposure to high phenylalanine levels [4].

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 120-360 μmol/L (2-6 mg/dL) for at least 3 months prior to 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 assure adequate weight gain during pregnancy [5].

Women with untreated PKU in the periconception period and the first trimester are at increased risk to have a fetus with multiple abnormalities due to the teratogenic effects of hyperphenylalaninemia. Uncontrolled maternal PKU leads to increased risk for maternal PKU syndrome, a constellation of findings that includes congenital heart disease, microcephaly, intrauterine growth restriction, and neurodevelopmental disability [6]. Platt and colleagues evaluated pregnancy outcomes in 576 women with hyperphenylalaninemia over a 12 year period as part of the Maternal Phenylketonuria Collaborative Study. The outcomes were classified according to the maternal phenotype and type 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 120-360 mmol/L.

This long-term study demonstrated that phenylalanine restricted diet before conception or by 8-10 weeks gestation significantly decreased the incidence of congenital heart disease and microcephaly in offspring of affected mothers. Maternal phenylalanine levels greater that 900 mmol/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 [7]. If mothers are unable to follow the recommended treatment guidelines to achieve target phenylalanine levels and have been shown to be responsive to sapropterin (Kuvan), consideration of its use should be strongly considered as it may assist in reaching phenylalanine targets. There is currently a registry available for all women who take this medication in pregnancy and participation should be strongly encouraged.

Natural protein is limited in the maternal PKU diet, although pregnancy increases the protein requirement, therefore protein requirements must be met with use of amino acid based medical foods [4]. Collaboration with a nutritionist can help ensure that women affected with PKU have adequate intake of protein, total fat and essential fatty acids, vitamins, and minerals.

Long-term neurodevelopmental outcomes in children born to mothers with PKU were investigated by Waisbren and colleagues 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 to controls, suggesting cognitive decline over time. However, long-term studies have not been performed to validate this finding [8].

Women with PKU should undergo serial ultrasound evaluations in pregnancy due to the high incidence of growth abnormalities. It is reasonable to consider performing a fetal echocardiogram due to the risk of congenital heart disease in this patient population [7]. There have been no studies indicating any effect of PKU on the labor and delivery process.

Women with PKU benefit from a multidisciplinary approach during the postpartum period. This time may prove challenging due to the high nutritional demands of lactation. Maintaining adequate nutritional needs while adhering to phenylalanine restriction may require use of supplementation and the aid of a lactation consultant, nutritionist and metabolic geneticist [4]

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. Carrier screening is possible for partners of affected women, and should be offered. CVS or amniocentesis can be performed for prenatal diagnosis if the underlying variants are known [3].

Fatty acid oxidation disorders

Fatty acid oxidation (FAO) disorders are a group of autosomal recessive disorders characterized by a deficiency in various enzymes in the metabolic pathway necessary for conversion of fats to energy. Mitochondrial fatty acid oxidation fuels hepatic ketogenesis and restores hepatic glycogen stores utilized 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 [9].

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 1:4,900 and 1:17,000. It is most prevalent among Native Americans and those of northern European descent. The onset of symptoms is typically between 3 and 24 months of age, but may present later in adulthood. Early diagnosis is possible with newborn screening. 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 [9].

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 LCHAD. Several authors have demonstrated that short and medium chain defects can be implicated in maternal liver disease during pregnancy as well [10,11]. Browning et al. demonstrated a 18.1-fold increase in maternal liver disease in pregnancies complicated by any fetal fatty oxidation disorder when compared with controls with unaffected fetuses [10]. In a prospective analysis by Ibdah et al., authors found that 15-20% of pregnancies complicated by AFLP and 2% of pregnancies with HELLP are associated with fetal LCHAD deficiency [12,13]. 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 [12]. 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 [14]. 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. Typically, after age 2, clinical manifestations may occur in the setting of fasting beyond 12 hours. 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 Caucasian population for MCAD deficiency; therefore a woman with FAO deficiency and her untested, non-consanguineous 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 however this is not currently available in the United States [9,15].

Chromosomal anomalies

There are many chromosomal anomalies that result in multiple clinical manifestations and preserved fertility. Due the varying clinical issues, each condition requires different surveillance in the antenatal period. Turner Syndrome is reviewed as there are complex cardiac issues that will impact pregnancy management.

Turner syndrome

Turner syndrome affects approximately 1 in 2500 live born females and results from complete or partial absence of the second X chromosome and may occur with or without mosaicism. Affected individuals possess varying degrees of 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 is often made in the prenatal period due to an early ultrasound finding of thickened nuchal translucency. Postnatal diagnosis should also be considered in females who have delayed puberty, primary infertility and/or growth failure, especially if any of the characteristic phenotypic findings are present.

Prenatal diagnosis and early identification of patients with Turner syndrome has allowed improved clinical care. Postnatal care is best achieved in a multidisciplinary manner, as it may require cardiologists, endocrinologists and geneticists at different times during development. 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. In contrast, women diagnosed with mosaic Turner syndrome may not encounter such high rates of delayed puberty or infertility. The use of estrogen therapy allows breast and uterine development; this treatment is most often coordinated under the care of a pediatric endocrinologist [16,17].

Due to 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. Bernard et al. (2016) examined spontaneous pregnancy and fertility rates in 480 women with TS. In this cohort, 27 had a total of 51 pregnancies. 31% ended in miscarriage, while 58% were term pregnancies. Of these, approximately 20% were complicated by hypertensive disorders of pregnancy [18,19]. Preconception counseling in women with TS who do decide to proceed with ART should stress single embryo transfer given the increased medical risks associated with multiple gestations coupled with the additional risks that occur in these patients.

The prevalence of cardiac disease in women with Turner syndrome ranges from 25-50%. The most common cardiac conditions include hypertension, bicuspid aortic valve, dilated ascending aorta and coarctation of the aorta [20,21]. Due to these potential complications, women with Turner syndrome should undergo a comprehensive cardiac evaluation prior to assisted reproduction or conception [20–23]. It has been suggested that contraindications to pregnancy include previous aortic coarctation or dissection, and aortic size >25 mm/m^2 (aortic size index >2.5 cm/ m^2). Aortic dissection in pregnancy is a recognized risk in women with TS, and has been reported in the setting of a normal aortic root . Aortic diameter should be adjusted to body surface area and measured at the ascending aorta. Karnis and colleagues concluded that maternal risk of death from rupture or dissection of the aorta in pregnancy may be 2% or higher [22]. If pregnancy is attempted in the presence of a cardiac anomaly, careful coordination with perinatology and cardiology should take place in the antepartum period. Management includes baseline maternal echo, strict blood pressure control and close surveillance to optimize maternal and fetal outcomes [20,24].

From an endocrine standpoint, women with Turner syndrome have an increased risk of diabetes and thyroid dysfunction and 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 (SHOX) gene, resulting in adult stature approximately 20 cm less than average female adult height [25,26]. 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 [18].

Fetal complications in women with Turner syndrome have been reported to include an increased rate of spontaneous abortion, fetal malformation and chromosomal anomalies [18,19,27]. 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 six that were conceived with ART, 3 resulted in infants with low birth weight [18]. Georgopoulos et al. also reported 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 an increased frequency of prenatal ultrasounds to monitor for growth is warranted [28].

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 prior to 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.

Single gene disorders

There are many single gene disorders that have clinically significant manifestations that need close surveillance in pregnancy. In this review, cystic fibrosis and various connective tissue disorders will be reviewed due to the impact of theses diseases on maternal health and risk for antenatal complications.

Cystic fibrosis

Cystic Fibrosis (CF) is an autosomal recessive disorder that results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The presence of two disease causing mutations in the CFTR gene results in dysfunction of the cystic fibrosis transmembrane conductance regulator located on epithelial cell membranes.

Compromised epithelial cell function of the respiratory tract, exocrine pancreas, sweat glands, intestine and hepataobiliary system result in the various clinical manifestations commonly observed in CF. The major cause of morbidity in CF patients is due to pulmonary disease. Impaired clearance of thickened mucous in the upper airway leads to recurrent sinopulmonary infections resulting 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 cystic fibrosis related diabetes mellitus, observed with increasing incidence in adult patients with CF. Meconium ileus in observed in approximately 20% of newborns [29].

Improvements in managing the chronic medical issues that CF patients face has resulted in an increasing number of those affected reaching adulthood. As such, more women with varying degrees of disease severity are achieving pregnancy [30]. 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 are fertile with the rate of live births reported at 1.9 per 100 from age 13-45 years [31].

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

Women with cystic fibrosis 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 U.S. 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 in these reports, although this was not the primary outcome of the study. 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 instrumental in patients with CF who experience malabsorption due to pancreatic insufficiency [31,32].

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 improve their overall nutritional status in pregnancy. Despite this, the increased resting energy expenditure, in addition to malnutrition, result 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 prior to conception. Patients with CF are susceptible to cystic fibrosis related diabetes (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 prior to conception. Balancing the competing issues of increasing maternal weight gain while managing CFRD is complex and employing the aid of a nutritionist familiar with CF is critical [30].

The pulmonary issues facing women with cystic fibrosis 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 FEV1 > 60 percent, do not have significantly increased maternal morbidity in pregnancy. In contrast, 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 (PFTs), 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 [33,34].

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 [30,33,35,36]. Limitations of the labor and delivery process will likely be determined by the underlying pulmonary function. Consultation with anesthesiology prior to labor is advisable, particularly in patients with underlying pulmonary or cardiac dysfunction.

Cesarean delivery is not recommended unless necessary for obstetric indications [34,37]. A more recent review by Girault and colleagues (2016) suggested improved outcomes compared to those previously published. This group performed a retrospective cohort study to compare maternal and perinatal outcomes in 33 pregnancies in women with CF compared to healthy women. Median gestational age at delivery was similar at 38 weeks. Mode of delivery was also similar between groups. Neonatal outcomes were similar as well, with no statistical difference in birth weight, APGAR scores, or length of hospitalization [38].

Genetic counseling is important during the preconception period given the risk of recurrence. Offspring of women with CF are obligate heterozygotes. Due to the high carrier frequency in certain populations, there is a considerable likelihood for heterozygous status in the partner, increasing the chance of having an affected infant. Determining the 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 due to limitations of testing. CFTR sequencing is available but is not appropriate in all cases. Prenatal diagnosis is available via CVS and amniocentesis, although parental CFTR mutations must be identified to allow prenatal testing [29].

Marfan syndrome

Marfan syndrome is an autosomal dominant disorder that is reported to occur in 2-3 per 10,000 individuals, with no ethnic or gender predisposition. Approximately 25% of cases are sporadic, due to *de novo* mutations. FBN1 encodes fibrillin 1, an extracellular matrix glycoprotein. Fibrillin 1 normally polymerizes to form microfibrils. Fibrillin microfibrils function as a scaffold that promotes structural integrity in a variety of tissues, including the aorta, lens, and skin, among others. When there is a genetic variant, the abnormal fibrillin 1 inhibits normal formation and thus stability and function of the various tissues in which this microfibril is found. These structural alterations in the extracellular matrix are responsible for the disease manifestations in classic Marfan syndrome [39].

Marfan syndrome is a characterized by manifestations in multiple body systems, most often skeletal, cardiovascular, and ocular. Consensus diagnostic criteria for Marfan syndrome have been available since 1986 [40]. The skeletal manifestations commonly include long bone overgrowth causing tall stature, anterior chest deformity, vertebral column abnormalities, arachnodactyly and loose joints. Ocular abnormalities include ectopia lentis, flat cornea, myopia, and increased globe length. Cardiovascular manifestations are the cause of increased morbidity in patients with Marfan syndrome, particularly in pregnancy. Cardiovascular findings include abnormalities of the heart and vasculature, including thickened atrioventricular valves causing varying degrees of regurgitation. This regurgitation can have downstream effects, including congestive heart failure and even pulmonary hypertension with mitral valve involvement. Aortic valve dysfunction has been observed, as has an increased incidence of arrhythmia. More commonly, cardiovascular issues are manifested by aortic aneurysm and dissection, typically as the aortic root dilates. The aortic root diameter and any family history of dissection are important in risk assessment.

Pulmonary findings in Marfan syndrome include apical blebs that increase risk for spontaneous pneumothorax, which occur in approximately 4-15% of patients. Skin findings increased in individuals with Marfan syndrome include striae atrophicae in areas not typically associated with increased distention. Additionally, there is also an increase in inguinal and surgical hernias. Women with Marfan syndrome have not been shown to have the increase in uterine rupture that can be seen in other connective tissue disorders such as Ehlers Danlos and Loeys-Dietz syndromes [41].

Women with Marfan syndrome do not typically have impaired fertility. Despite this, relatively few studies have reported on Marfan syndrome and pregnancy. In a retrospective observational study, Meijboom and colleagues described the outcome of 142 pregnancies in 63 women with Marfan syndrome [42]. There were 17 (15%) preterm deliveries ranging in gestational age from 20 to 32 weeks, attributed to a variety of causes including preterm premature rupture of membranes, cervical insufficiency, and iatrogenic delivery for maternal cardiac reasons. Primary cesarean section was performed in 14% of cases, with half of these due to maternal cardiac indications. The rate of gestational hypertension was slightly elevated at 8%, while the rates of preeclampsia and gestational diabetes were similar to the general population. In terms of fetal outcomes, there was no increase in morbidity above that in the general population. Fifty-three children were diagnosed with Marfan syndrome, three of whom had complications in the newborn period related to this diagnosis [42]. In a more recent retrospective cohort study by Hassan and collegues, they examined outcomes in 339 pregnancies in women with Marfan syndrome and compared outcomes to women without Marfan syndrome. They found an increased risk of cesarean and operative vaginal delivery compared to the control population. They did not identify a statistically significant increase in hypertensive disorders of pregnancy, preterm premature rupture of membranes, gestational diabetes, or postpartum hemorrhage. Neonatal outcomes were notable for an increased risk for preterm delivery, although due to the nature of the study, they were unable to identify gestational age of delivery. Additionally, there was an increased incidence of intrauterine growth restriction and small for gestational age infants in women with Marfan syndrome as compared to normal controls [43].

Significant maternal morbidity associated with pregnancy in Marfan syndrome is primarily due to the cardiovascular complications that may arise. Advances in medical and surgical interventions have increased the average life expectancy from 32 to 45 years, and enabled women who previously suffered from a severely compromised cardiac status to be well enough to conceive.

Physiologic changes of pregnancy result in an increased blood volume, which can cause exacerbation of underlying cardiac and vascular abnormalities. It is critical that women with Marfan syndrome who are planning to undergo pregnancy obtain an echocardiogram to evaluate aortic root size and evidence of valvular abnormality. Most studies support that if women have minimal cardiac disease with an aortic root diameter less than 40 mm, then pregnancy is typically well tolerated. However, a residual risk of 1% still exists for these women to develop aortic dissection, endocarditis or congestive heart failure despite a normal aortic root diameter. If significant aortic dilation is observed, at greater than 40 mm, women should be counseled that the risk of maternal mortality rises sharply. The European Society of Cardiology task force states that there is a risk of 10% for aortic dissection in this cohort of patients. These guidelines specifically suggest elective surgical repair prior to pregnancy for women with aortic root dimension greater than 4.7 centimeters [44].

In a prospective cohort study by Lilian et al, women with Marfan syndrome who had a mean aortic root diameter of 37 mm were observed. These investigators did not observe any significant difference in growth of the aortic root between the pregnancy group and the matched childless group during an observation period of 6 years. However, they did observe a significantly greater increase in aortic root diameter in pregnant versus nonpregnant women with baseline aortic root diameter greater than 40 mm [45]. Roman et al. examined aortic complications in women with Marfan syndrome in pregnancy by evaluating the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). They identified 227 pregnancies in 184 women. In this cohort, approximately 11% experienced pregnancy related aortic complications, including both type A and type B aortic dissections, coronary artery dissection and significant aortic growth; 75% of all dissections occurred in the postpartum period [46].

The use of beta-adrenergic receptor blocking agents is employed routinely in patients with Marfan syndrome to decrease the rate of aortic dilation and should be continued during pregnancy. Blood pressure should be strictly controlled with multiple agents (e.g. beta blockers with afterload reduction) if necessary. Close echocardiographic surveillance of aortic status should be performed at intervals of 4-6 weeks. If decompensation of maternal cardiac status is observed during the surveillance period, hospitalization and administration of steroids for fetal lung maturity should be considered after viability, as the risk of iatrogenic prematurity is increased. If there are symptoms of arrhythmia, evaluation via Holter or event monitor or even telemetry may be necessary. Coordination of care with a

cardiologist and anesthesiologist is critical for the optimal management of women with Marfan syndrome due to the potential for cardiac decompensation as well as the possibility of dural ectasia, which may complicate routine spinal anesthesia. Patients with a stable aortic root diameter less than 40 mm and lack of significant valvular disease are eligible for a planned vaginal delivery [20,47]. Left lateral positioning and epidural anesthesia are recommended during labor and delivery to prevent pain-mediated fluctuations in pulse and blood pressure. In women who present with preterm labor, magnesium sulfate, indomethacin, and nifedipine are acceptable for neuroprotection and or tocolysis if necessary. Beta adrenergics such as terbutaline should be avoided. The second stage should be shortened with consideration of an operative delivery to minimize maternal expulsive efforts. Women with Marfan syndrome and aortic dilation greater than 40 mm, or with significant valvular disease should be counseled to undergo primary cesarean delivery as labor and delivery may be hemodynamically stressful and promote aortic dissection. The increased blood volume and hemodynamic changes of pregnancy do not resolve until approximately 6 to 8 weeks postpartum therefore, cardiac status (e.g with beta blockade) should continue to be observed closely during this period [44].

Aortic dissection in a woman with Marfan syndrome requires coordinated management by cardiothoracic surgery, anesthesiology and maternal fetal medicine. The 2010 ACC/AHA/AATS guidelines provided recommendations for management of Marfan syndrome. They advise that if a Type A dissection occurs in the first or second trimester, surgical repair should be performed urgently with fetal monitoring if possible. If a type A dissection occurs during the third trimester, aortic repair following cesarean delivery is advised. If a type B aortic dissection occurs, medical therapy is recommended if no other complications are present [48].

Women with Marfan syndrome should be counseled that, in addition to the obstetric and cardiovascular risk, there is the 50% risk for having an affected child due to the autosomal dominant transmission of this disorder. Prenatal diagnosis via chorionic villus sampling or amniocentesis is available if the disease-causing allele has been identified. Preimplantation genetic diagnosis is also available if the variants are known. It is important to ensure that the family understands that the severity of the phenotype can vary greatly within a family [49].

Loeys-Dietz syndrome

Loeys Dietz is a syndrome with phenotypic similarities to Marfan syndrome but with additional distinctive features that are critical to appreciate for effective obstetric management. This syndrome is inherited as an autosomal dominant disorder, although 75% of cases arise due to de novo mutations. Mutations in TGFBR1 and TGFBR2 are implicated in this disease; these mutations result in abnormal TGF beta-receptors that in turn lead to altered downstream signaling pathways. This ultimately results in abnormal composition of vascular walls with an increased tendency for dilation and dissection of the vessel wall [50].

Clinical manifestations of LDS are primarily vascular, skeletal, craniofacial, and cutaneous. Approximately 75% of those affected with LDS have type 1 LDS. In terms of vascular disease, there is high incidence of dilatation of the aorta (reported to present in 95% of those affected) leading to an increased risk for aortic dissection and rupture. Mitral valve prolapse and enlargement of the proximal pulmonary artery are also present. Due to these clinical manifestations, LDS is often referred to as a familial thoracic aortic aneurysm syndrome. Skeletal findings include pectus excavatum, joint laxity, scoliosis, and arachnodactyly. Ocular hypertelorism, bifid uvula or cleft palate and craniosynostosis can be observed in this group of patients. Those affected with LDS type 2 exhibit vascular, skeletal and cutaneous findings. Cutaneous features include translucent skin, increased tendency to bruise, and dystrophic scars [51].

Loeys-Dietz was only recognized as a syndrome in 2005, and the management in pregnancy is not yet well described. Most mortality is related to cardiovascular findings, which are similar to those seen in Marfan syndrome patients. These patients differ from those with Marfan syndrome in that they are at increased risk for dissection even if no progressive aortic enlargement has been observed, and the absolute risk for these patients cannot be quantified. Women with LDS should be followed with interval echocardiograms for surveillance of aortic dimension at baseline and every 4-6 weeks during pregnancy. Patients are predisposed to aneurysms of other vessels, including the subclavian, renal, superior mesenteric, hepatic, and coronary arteries. Therefore, other imaging modalities such as CT or MRI with contrast may need to be considered for surveillance [52]. Cauldwell and colleagues (2016)

proposed a management protocol for women with LDS that includes prepregnancy cardiac and cerebral imaging. Just as in Marfan syndrome, pregnancy should be avoided if the aortic diameter is 40 mm or greater. However, it is difficult to quantify the risk of dissection in this cohort of patients. Blood pressure monitoring and use of beta blockers should also be considered [53]. In a recent case series by Braverman and colleagues (2016), they report outcomes in 3 women with LDS who underwent elective aortic root replacement due to aneurysmal disease and subsequently become pregnant. Despite adequate surveillance and use of beta blockers, 2 of these women underwent acute aortic dissection in the postpartum period [54].

The cutaneous findings of LDS are similar to those observed in the vascular type of Ehlers Danlos syndrome (EDS), although these are distinct disorders and the underlying gene mutations differ. With the cutaneous similarities, there is likely an increased risk for preterm premature rupture of membranes, uterine and bowel rupture, and extensive vaginal and perineal tears, as occur in those with EDS, although these complications have not been well documented to occur in LDS patients. The effect of LDS on the fetus is unknown at this time.

Women with LDS who are considering pregnancy should be counseled that a relative paucity of medical literature makes it difficult to give exact risk quantification. However, those with a more complicated cardiac status at baseline appear to be at markedly increased risk for morbidity and mortality during pregnancy and therefore should be counseled accordingly.

LDS is an autosomal dominant disorder; therefore patients should be counseled regarding the 50% transmission rate to their offspring. Prenatal diagnosis is possible with analysis of fetal DNA obtained from CVS or amniocentesis if the disease causing mutation in the mother has been identified [55].

Ehlers Danlos syndrome

Ehlers Danlos Syndrome (EDS) represents a heterogeneous group of connective tissue disorders with various patterns of inheritance and differing genetic mutations. Incidence varies based on the type but is approximately 1 in 5000 as a group. The current scheme for categorization for Ehlers Danlos involves grouping into various types including classic, hypermobility, vascular, kyphoscoliotic, arthrochalasia, dermatosparaxis, and cardiac valvular types.

The cardinal manifestations exhibited in Ehlers Danlos classic type include joint hypermobility, skin hyperextensibility, and abnormal wound healing. There is autosomal dominant inheritance for this subtype of EDS, and at least 50% of affected individuals have a defect in COL5A1 or COL5A2.

Diagnostic criteria for classic type EDS include a combination of family history and clinical characteristics. Major diagnostic criteria include skin hyperextensibility, atrophic scars, and joint hypermobility as assessed by Beighton's criteria [57,58]. Adverse obstetric outcomes are common in patients with EDS classic type, with an increased risk for preterm premature rupture of membranes, severe perineal lacerations, and postpartum hemorrhage.

Vascular EDS, also called EDS type IV, is inherited in an autosomal dominant pattern, and is caused by a mutation in COL3A1 resulting in abnormal type III procollagen production. This leads to characteristic findings including translucent skin, and increased tendency to bruise. Further, increased fragility of the arteries, intestines, and uterus leads to an increased rate of rupture of these entities. Aneurysm or AV fistula may be present prior to rupture although rupture can take place spontaneously [58]. Those with vascular EDS require multidisciplinary management during pregnancy due to the significant associated cardiovascular manifestations and adverse obstetric outcomes, with a high incidence of morbidity and mortality.

Pepin et al reviewed 183 pregnancies in 81 women with EDS type IV. In this cohort, there were 167 live born infants, 3 stillbirths, 10 spontaneous abortions and 3 therapeutic abortions. The maternal mortality rate was approximately 15%, as twelve of the 81 women died in the peripartum or postpartum period in this cohort. The causes of death included uterine rupture during labor in five women, and great vessel rupture in 7 women, two during labor and five in the postpartum period [59]. Murray et al. (2014) investigated maternal mortality and morbidity in 565 pregnancies in women with vascular EDS using retrospective pedigree data and information collected during structured interviews. Pregnancy related death occurred in 5% of all deliveries. Commonly occurring complications included third and fourth degree lacerations and preterm delivery. Severe complications occurred in approximately

15% of deliveries including arterial rupture, uterine rupture, and surgical complications such as hemorrhage and wound dehiscence [60].

The mode of delivery for patients with Ehlers-Danlos type IV requires extensive counseling as there is significant risk associated with both vaginal and cesarean delivery. The increased risk of uterine rupture has contributed to the general recommendation for cesarean delivery prior to the onset of labor. The timing for delivery has ranged in the literature with recommendations for delivery as early as 32 weeks gestation by Lurie et al. to 34 to 36 weeks gestation [61–63]. Patients are at risk for severe postpartum hemorrhage, therefore consultation with anesthesia is recommended. Recent case reports have documented early cesarean section with use of desmopressin to prevent bleeding complications. Desmopressin stimulates the release of von Willebrand factor (vWF) from the endothelial cells. The increase in vWF improves coagulation. Because of poor tissue integrity, incisions typically have delayed healing and increased tendency for wound dehiscence. Therefore, the use of retention sutures that remain in place for at least 14 days is recommended. Other important obstetric complications include increased rates of preterm premature rupture of membranes although precise incidence rates are not available [61].

Patients with Ehlers Danlos should be counseled carefully, ideally in the preconception period. If pregnancy is desired, preconception cardiology evaluation is necessary. Close monitoring of vascular status is advised including evaluation of aortic size and to identify presence of aneurysms. Multidisciplinary management with cardiology and maternal fetal medicine is necessary. It is critical to know the type of EDS as each is associated with varying manifestations, and inheritance patterns. Prenatal diagnosis with analysis of fetal DNA obtained by CVS or amniocentesis is available if there is prior knowledge of the disease causing mutation [56,58].

Summary

Women with genetic disorders are increasingly reaching reproductive age, and many become pregnant. While some women can tolerate pregnancy and have successful outcomes, for others pregnancy may carry a high risk of morbidity and mortality. A multidisciplinary approach, with careful attention to individual risks, is critical to management. Ideally, preconception consultation should be recommended to review maternal, perinatal, and neonatal risks, including recurrence risk to offspring.

Practice points

- The cardiovascular manifestations in Turner syndrome, Marfan syndrome, Loeys Dietz, and vascular type EDS require close co management with perinatology, cardiology and genetics in the preconception period and throughout the pregnancy.
- Women with PKU need close adherence to Phe-restricted diet to ensure that Phe levels stay within target range to avoid both maternal decompensation and congenital defects.
- Women with Turner syndrome may have risk for aortic dissection at a significantly smaller aortic size than in women with Marfan syndrome (25 mm compared to 40 mm).
- Women with cystic fibrosis can vary in their clinical presentation therefore those with severe pulmonary disease and resulting pulmonary hypertension should be counseled regarding the significant associated maternal morbidity if pregnancy is attempted.
- There is significant risk for adverse maternal and pregnancy outcomes in women with vascular type Ehlers Danlos however this is not true for all types of EDS therefore identification of the type of EDS is critical.

Research agenda

- Molecular genetic testing for all types of EDS
- Criteria for evaluation for neonatal Marfan syndrome
- Risk stratification for pregnancy for women with Turner variants

Conflicts of interest

None.

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