Cardiovascular Diseases of Genetic Etiology and Implications for the Pregnant Woman

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Abstract

Pregnancy presents a unique hemodynamic challenge to women with cardiovascular disorders of genetic etiology. Many such women undergo decompensation during pregnancy or have acute cardiac events. In addition, there is a risk of transmission of the disease to the fetus, which warrants prenatal testing using invasive and noninvasive means. This article provides an overview of the management issues of these women during pregnancy.

Keywords
- Marfan's syndrome
- preconceptional counseling
- genetic counseling
- pregnancy management
- intrapartum management
- Turner's syndrome
- cardiomyopathies
- inherited arrhythmias

Introduction

The exact prevalence of pregnancy-related cardiovascular diseases is not well known; however, these disorders are one of the leading causes of maternal mortality during pregnancy especially in the developed nations.[1,2] Although most of these conditions are of multifactorial or acquired origin, some may be of genetic etiology, arising due to chromosomal abnormalities, copy number defects, or single-gene disorders. With advances in medical care, many female patients with genetic cardiovascular disorders are reaching adulthood and becoming pregnant. During pregnancy, in view of unique hemodynamic milieu, there can be decompensation events or acute cardiac mishaps requiring intensive management. Also, in view of the genetic abnormality, there is a risk of the fetus being similarly affected, and this necessitates genetic counseling and prenatal diagnosis. In addition, various maternal drugs may have teratogenic or other compromising effects on the developing fetus. These concerns together make the management of these cases challenging.[3,4] The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC) has published guidelines for management of cardiovascular disorders during pregnancy, inclusive of those with genetic basis.[5]

Cardiovascular Disorders of Genetic Etiology

Most cardiovascular disorders are of multifactorial etiology, and genetics does not play a major role in their causation. However, certain conditions show predominant genetic basis. These are as follows:

- **Aortopathies:** Various syndromic entities such as Marfan's syndrome, Turner's syndrome, and other rarer connective tissue disorders such as Loeys Dietz syndrome, vascular Ehlers-Danlos syndrome, etc. as well as nonsyndromic hereditary forms constitute this group. Most of these conditions show autosomal dominant inheritance pattern. Occasionally, aortic abnormalities may occur with other congenital heart defects such as coarctation or bicuspid valve or as a nonheritable aortic pathology.[5–7]

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- **Cardiomyopathies (CM):** There is a strong genetic basis of CMs with at least 40 to 60% of hypertrophic CM (HCM), 17 to 30% of dilated CM (DCM), and up to 60% of arrhythmogenic right ventricular cardiomyopathy (ARVC) showing a single-gene etiology.[8] Many of these CMs show autosomal dominant inheritance and have 50% recurrence risk in the fetus.
- **Inherited arrhythmias:** Long QT syndrome is the most common inherited arrhythmia, showing autosomal dominant inheritance and arising due to mutations in at least 20 different genes.[9]
- **Congenital heart defects (CHDs):** Although most CHDs are of multifactorial origin, conotruncal defects result from 22q11.2 deletion in a significant number of patients. Besides raising management difficulties, this is associated with a 50% recurrence risk in the fetus. Noonan's syndrome can present with cardiac defects such as pulmonary stenosis and HCM in a pregnant woman. Some nonsyndromic cardiac defects may also occasionally occur due to single-gene defects such as *NKX2–5*, *GATA4* mutations in septal defects, and *TFAP2B* variants in patent ductus arteriosus.[10]
- **Familial hypercholesterolemia (FH):** This has a prevalence of 1:500 in the population, and predisposes the individual to premature atherosclerosis and ischemic heart disease. Heterozygous mutations in *LDLR*, *PCSK9*, and *APOB* can result in this condition. Inheritance is autosomal dominant with 50% recurrence risk in offspring.[11]

►**Table 1** lists the common genetic cardiovascular disorders and the associated relevant issues in pregnancy.

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the ESC guidelines recommends the use of the mWHO (modified World Health Organization) classification for assessment of the maternal cardiovascular risk for these women in the prepregnancy period, and depending on this, the subsequent pregnancy management is designed.[5] A baseline evaluation includes an electrocardiogram (ECG), echocardiography, and exercise test. Other evaluations are individualized depending on the underlying condition. Women need to be counseled during this period regarding the risk of pregnancy complications such as preterm labor, fetal growth restriction, postpartum hemorrhage, and risk of maternal cardiac event that can vary from 2.5 to 5% for women in mWHO I category to 40 to 100% for women in mWHO IV category.[5] For all women in mWHO IV category, pregnancy is contraindicated and termination of pregnancy should be considered in case of unplanned conception.[5] All women in mWHO II–III, III, and IV categories should undergo pregnancy management at an expert center under care of a multidisciplinary pregnancy heart team constituting an obstetrician, anesthetist and cardiologist.[5] Management and monitoring need to be individualized as per the underlying condition and is detailed in the following section. Computed radiography and cardiac catheterization need to be avoided during pregnancy due to risks associated with ionizing radiation exposure to the fetus. There is 18 to 30% risk of various fetal complications such as prematurity, growth restriction, transmission of maternal disease, and 1 to 4% risk of neonatal mortality.[5,12]

Table 1 Genetic cardiovascular diseases of significance during pregnancy

Disease	Significance
Aortopathies	Risk of aortic dissection during pregnancy More common in third trimester (50%) and postpartum period (33%) 50% risk of transmission for Marfan's syndrome, Loeys–Dietz syndrome Risk of uterine rupture in vascular Ehlers–Danlos syndrome Other issues: Arrhythmias, mitral regurgitation, dural abnormalities, heart failure Short stature, diabetes in Turner's syndrome
Arrhythmias	Sudden cardiac event during pregnancy or labor Transmission of arrhythmia to fetus predisposing to in utero demise or sudden infant death syndrome (SIDS) Teratogenic antiarrhythmic drugs
Cardiomyopathies	Risk of cardiac decompensation: Dilated cardiomyopathy (DCM) Risk of sudden cardiac depth during labor: Hypertrophic cardiomyopathy (HCM) Risk of arrhythmia and thromboembolism Risk of inheritance to fetus
22q deletion syndrome	Risk of decompensation in uncorrected lesions 50% risk of transmission to fetus
Familial hypercholesterolemia	Risk of acute ischemia for women with preexisting plaques 50% risk of transmission to fetus
Noonan's syndrome	Risk associated with underlying cardiac lesion 50% risk of transmission to fetus

Course during Pregnancy and Management

- **Aortopathies:** The increased cardiac overload during pregnancy and mesenchymal changes in the aortic wall predispose these patients to progressive aortic dilatation during pregnancy, and this can result in catastrophic events such as aortic dissection.[3–6,13,14] Patients with preexisting aortic dilatation are more likely to show progression to dissection. Various studies have shown at least 4% risk of aortic dissection in patients with Marfan's syndrome during pregnancy. Women most likely to have this complication are the ones with aortic root dimension of > 45 mm (mWHO class IV), where 10% pregnancies are complicated by aortic dissection resulting in maternal mortality. Women with prepregnancy aortic root diameter < 40 mm have up to 1% risk of acute dissection. There is also up to 40% risk of various obstetric complications including preterm rupture of membranes and intrauterine growth restriction.[3–6] Up to 33% of women with Turner's syndrome have aortic valve abnormalities, such as bicuspid aortic valve and coarctation, and this is associated with a

100-fold increase in risk of dissection compared with other women. An aortic size index of > 25 mm/m^2 is reported to increase the risk of dissection.[6,7,13] Individuals with relatively rare genetic disorders, Loeys-Dietz syndrome, and familial thoracic aortic aneurysm and dissection (FTAAD) are also at risk of catastrophic events during pregnancy. For such women, the ESC and the American Heart Association (AHA) have provided guidelines for management in prepregnancy period as well as during pregnancy.[5,6,14] These are summarized in ►**Table 2**. The rationale behind the guidelines is to perform aortic repair prior to conceiving in the high-risk group, to continue β-blocker therapy and monitoring during pregnancy for the others, and to deliver by cesarean section in those at risk for dissection due to the hemodynamic changes during labor. Women with vascular Ehlers-Danlos syndrome are in addition at risk of uterine rupture. Pregnancy is ideally contraindicated in such women, and if they are pregnant, they have to be delivered by cesarean section.[5,6,14] Emergency surgery for aortic repair is indicated for women with progressive aortic dilatation or type A dissection. This is associated with a 20 to 30% risk of fetal mortality.[5] Hence, in such a scenario, a viable fetus should be delivered prior to or along with maternal surgery; a nonviable fetus should be considered for termination.

- **Inherited arrhythmias:** The hemodynamic and hormonal changes in pregnancy make it a potentially proarrhythmic state.[3,4] Various factors such as increased myocardial stretch, increased catecholamine activity, greater myocardial excitability, and cardiac contractility are observed and contribute to this situation. Atrial extrasystoles, supraventricular tachycardia, atrial flutter and fibrillation, and ventricular tachycardias have all been reported in pregnant women with increased frequency.[15] Inherited arrhythmias that are associated with increased risk during pregnancy include the long QT syndrome and Brugada's syndrome. In women with long QT syndrome, more commonly type 2, there is a 2.7 times increased risk of ventricular tachyarrhythmias (VT), which is more prominent in the postpartum period up to 9 months post delivery. Rare events of unstable VT have also been reported in Brugada's syndrome.[15] Sudden death may be the only manifestation of diseases in some instances. Hence, prepregnancy stabilization on nonteratogenic antiarrhythmic drugs is essential for these women.[5,15] β-Blockers are the primary drugs recommended. They act through adrenergic blockade, which reduces the risk of arrhythmias, and through reducing the QT interval. Additionally, prepregnancy assessment should be done to ascertain whether the woman requires a pacemaker or intracardiac defibrillator.[5,15] During pregnancy, antiarrhythmic medication and regular monitoring need to be continued. ECG is recommended at baseline, at 7 months' gestation, and 2 to 3 months postpartum.[5] Telemetry has been recommended in intrapartum period to avoid precipitation of acute VT, and postpartum antiarrhythmic therapy should continue. The risk to transmission to fetus for long QT syndrome is 50%, and prenatal diagnosis is possible at 11 to 12 weeks' gestation if molecular testing of the mother is available. If molecular testing is not possible, fetal ECG should be considered. Identification of an affected newborn at birth is also of utility for prevention of sudden infant death syndrome (SIDS).[15] This can be done using ECG or molecular testing if the mutation in the mother is known.
- **Cardiomyopathies:** Women with CM, including HCM, DCM, ARVC, and left ventricular noncompaction are at increased risk during pregnancy for adverse events such as heart failure, arrhythmias, thromboembolic accidents, and sudden cardiac death.[3,4,13] Women who are already in NYHA class III/IV heart failure or have severe left ventricular (LV) dysfunction (ejection fraction [EF] < 40%) prior to pregnancy or those with significant outflow tract obstruction due to hypertrophic CM should ideally be advised against pregnancy.[4,5] Management during pregnancy involves administration of diuretics to reduce volume overload, β-blocker therapy, and vasodilator therapy for women with DCM, along with anticoagulation using low-molecular-weight heparin (LMWH) in those with atrial fibrillation.[5,13] Antiarrhythmic drugs need to be used as required. Women with HCM are at risk of sudden cardiac events due to increased afterload, more commonly during labor. Continuous monitoring during pregnancy and intrapartum period is required for all women with CMs, and this should include an ECG and echocardiography, at least baseline and at 7 months' gestation, and intrapartum close hemodynamic surveillance. Delivery should be by vaginal route, preferably shortened by vacuum or forceps application, and cesarean section should be limited for obstetric indications.[5,13]
- **22qdeletion syndrome:** Pregnancy in women with 22qdeletion syndrome can be complicated by prematurity, growth restriction, and maternal morbidities related to cardiac defect, endocrine problems, and psychiatric issues.[16] In addition, there is 50% risk of the fetus being similarly affected, and in view of known phenotypic variability, the child's phenotype may be more severe than the mother.[17] Preconception counseling regarding these issues is important for these women. Appropriate nonteratogenic drugs, as required for cardiac lesion, should be started prepregnancy. Workup and management for endocrine problems such as hypoparathyroidism, hypothyroidism, and diabetes are also advised in the preconception period.[16] During pregnancy, prenatal diagnosis is performed at 11 to 12 weeks of gestation by chorionic villus sampling followed by MLPA/FISH (multiplex ligation-dependent probe amplification/fluorescence in situ hybridization) for 22q deletion.[17] Women with uncorrected cardiac defects need to be kept under surveillance and managed using drug therapy as required. Intrapartum care is also tailored depending on cardiac status.
- **Familial hypercholesterolemia:** Women with FM are at risk of ischemic heart disease, and this may rarely present in pregnancy with myocardial infarction. Regular monitoring of serum cholesterol levels is important for this group of patients, and this should continue postpartum till at least 6 weeks.[3] However,

Table 2 Summary of management guidelines

Disease	Prepregnancy	Pregnancy	Postpartum
Marfan's syndrome	Avoid pregnancy if aortic diameter > 45 mm Aortic repair surgery if aortic diameter > 40–45 mmStop ARBs Shift to β-blocker FBN1 sequencing for identification of mutation Counseling regarding risk of dissection	4–12 weekly aortic root diameter monitoring by transthoracic echo/MRI β–Blocker therapy Hypertension management Elective surgery for progressive dilatation Emergency surgery in case of type A dissection Monitoring in case of type B dissectionPND at 11–12 wk by chorionic villus sampling Cesarean section for women with aortic diameter > 40 mm, or women with acute/chronic dissection Epidural anesthesia and vacuum extraction for vaginal delivery	Continue same management as during pregnancy till 3–6 mo postpartum
Loeys–Dietz syndrome	Same as above	Same as above	Same as above
Turner's syndrome	Pregnancy to be avoided in women with coarctation of aorta and aortic dilatation Echocardiography and MRI–based evaluation of entire aorta Elective aortic repair if aortic size index > 25–27 mm/m^2	4–12 weekly monitoring of aortic root diameter Cesarean section in women with aortic root index > 20/25 mm/m^2 Hypertension management	–
Vascular Ehlers–Danlos syndrome	Pregnancy contraindicated	4–6 weekly monitoring of aortic root diameter Celiprolol therapy Elective surgery for progressive dilatation Elective cesarean section	Continue same management as during pregnancy till 3–6 mo postpartum
Inherited arrhythmias	Antiarrhythmic drugs—drugs with teratogenic potential need to be substituted with safer drugs Nonselective β-blockers for long QT syndrome ICD/pacemaker Discuss regarding up to 50% recurrence risk	ECG—baseline and at 7 mo β–Blockers ICD if indicated PND at 11–12 wk by CVS if maternal mutation identified	Continue β-blockers Neonatal ECG or targeted mutation analysis if PND not done
Cardiomyopathies	Drug therapy for heart failure and arrhythmias Switch to β_1-selective blockers Thromboprophylaxis for women with atrial fibrillation Teratogenic drugs to be stopped DCM: Pregnancy contraindicated if LVEF < 40% or NYHA class III/IV HCM: Pregnancy contraindicated if severe symptomatic outflow obstruction Prepregnancy septal ablation or septal myectomy Consider ICD if indicated	ECG, echocardiography baseline Monitoring during pregnancy as per severity: monthly to trimester wise β–Blockers Anticoagulation for women with arrhythmias Cardioversion or ICD implantation as indicated Intrapartum telemetry Cesarean section for HCM with severe obstruction or severe heart failure Avoid hypovolemia in HCM Assisted vaginal delivery for rest Prenatal diagnosis at 11–12 wk by CVS if maternal mutation identified	Continue surveillance till 3 mo postpartum Neonatal ECG, Echocardiography if PND not done Avoid lactation in women already in failure

(continued)

Table 2 *(continued)*

Disease	Prepregnancy	Pregnancy	Postpartum
22qdeletion syndrome	Baseline endocrinology and cardiac assessment Treatment as indicated depending on the functional class and clinical issues	Prenatal diagnosis by CVS at 11–12 wk followed by FISH/MLPA Monitoring during pregnancy and intrapartum period if uncorrected cardiac lesion	–
Familial hypercholesterolemia	Stop statins and lipid–lowering drugs 3 mo prior to conception	Dietary management, monitor cholesterol levels, and symptomatically	No consensus regarding lipid–lowering drugsAvoid
Other congenital heart diseases	Plan management as per mWHO classification Treatment as indicated depending on the functional class and clinical issues	Individualized management as per underlying defect and functional class Fetal echocardiography for prenatal diagnosis	–

Abbreviations: ARB, angiotensin II receptor blocker; CVS, chorionic villus sampling; DCM, dilated cardiomyopathy; ECG, electrocardiogram; FISH, fluorescence in situ hybridization; HCM, hypertrophic cardiomyopathy; ICD, implantable cardiac–defibrillator; LVEF, left ventricular ejection fraction; MLPA, multiplex ligation–dependent probe amplification; MRI, magnetic resonance imaging; mWHO, modified World Health Organization; NYHA, New York Heart Association; PND, prenatal diagnosis.

the management is challenged by the teratogenic potential of the lipid-lowering drugs. Statins are classified as category X drugs and are contraindicated during pregnancy. Niacin and ezetimibe are category C drugs. Women desirous of being pregnant should be advised to stop all these drugs at least 3 month prior to conceiving.[18] There is a 50% recurrence risk for FH in the offspring, but in view of the adult onset of disease and good response to therapy, prenatal invasive testing is usually not considered.

- **Other syndromic/nonsyndromic congenital defects:** These patients need to be managed as per the specific underlying defect and the mWHO class.[5] In cases, where the cardiac defect is part of a genetic syndrome, there could be other extracardiac issues that may need to be taken care of. For example, in Noonan's syndrome, women often have short stature, which could result in cephalopelvic disproportion during delivery; some women may develop coagulopathy, and rarely there could be complications due to a coexisting renal anomaly.[19] Hence, besides the management of the cardiac lesion, it is important to be aware of other potential complications of a specific syndrome. Recurrence risk for Noonan's syndrome in the offspring is 50%, and prenatal diagnosis is advised by invasive fetal sampling and targeted testing of the maternal mutation.[19] In view of the genetic heterogeneity and multifactorial nature of majority of nonsyndromic cardiac defects,[10] the maternal genetic defect may not be established in many such cases, but there is a risk of recurrence in the fetus, and hence prenatal diagnosis by fetal echocardiography is recommended between 20 and 24 weeks' gestation.

►**Table 2** briefly summarizes the management guidelines for genetic cardiovascular disorders in the preconception, pregnancy, and postpartum phases. ►**Table 3** summarizes the genetic testing strategies for these conditions.

Table 3 Summary of genetic testing approaches

Genetic disorder	Genetic testing	Prenatal diagnosis
Marfan's syndrome	FBN1 sequencing	CVS or amniocentesis followed by targeted mutation testing by sequencing
Vascular Ehlers–Danlos syndrome	COL3A1 sequencing	Same as above
Loeys–Dietz syndrome	TGFBR1 and 2 sequencing	Same as above
Turner syndrome	Karyotype	Amniocentesis followed by fetal karyotype
Cardiomyopathy	NGS–based panel testing for cardiomyopathy genes	CVS or amniocentesis followed by targeted mutation testing by sequencing
22q deletion	MLPA or FISH for 22q deletion	CVS or amniocentesis followed by MLPA or FISH for 22q deletion
Other CHDs	NGS–based panel testing if multiple affected family members	Fetal echocardiography at 20–24 wk
Noonan's syndrome or other syndromic CHDs	NGS–based panel testing or Sanger sequencing of the specific gene/s	CVS or amniocentesis followed by targeted mutation testing by Sequencing
Familial hypercholesterolemia	Sequencing of LDLR, PCSK9, and APOB	–

Abbreviations: CHD, congenital heart defect; CVS, chorionic villus sampling; FISH, fluorescence in situ hybridization; MLPA, multiplex ligation–dependent probe amplification; NGS, next–generation sequencing.

Conclusion

Pregnancy poses unique challenges to women with genetic cardiovascular diseases, and management in such cases needs to be tailored as per available guidelines. The primary concerns center around the impact of pregnancy on the lesion, and the complications arising secondary to this, that is, the risk of transmission to the fetus and the potential teratogenic effect of drugs used for cardiac management. It is important for these women to be managed by multidisciplinary teams in well-equipped cardiac units. In view of risk of transmission to the fetus, a genetic consultation for appropriate counseling and facilitating prenatal diagnosis is also warranted for these patients.

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Conflict of Interest Statement
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