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REVIEW PAPER

At the Heart of the Pregnancy: What Prenatal and Cardiovascular Genetic Counselors Need to Know about Maternal Heart Disease

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Abstract In the last decade, an increasing number of cardiac conditions have been shown to have a genetic basis. Cardiovascular genetic counseling has emerged as a subspecialty aiming to identify unaffected at-risk individuals. An important sector of this at-risk population also includes expectant mothers, in whom unique clinical challenges may arise. Genetic counselors, especially those in cardiovascular and prenatal settings, have an opportunity to identify and assist women who may benefit from cardiovascular care during pregnancy. This paper provides basic management and genetic evaluation principles for affected women, as well as guidance on identifying those who are at risk. We provide considerations for cardiac surveillance in pregnancy and the post-partum period. Finally, key psychosocial issues that appraise how to best provide support to at risk women as they make informed decisions are discussed. We propose that a team approach including cardiology, maternal fetal medicine, and genetic counseling best serves this patient population. Ongoing questions addressing an evidence based approach to cardiovascular genetic conditions in pregnancy still remain. Thus, well-designed research protocols are essential to mark progress in this area.

Keywords Cardiovascular genetics · Prenatal genetics · Cardiomyopathy · Channelopathy · Aortopathy · Connective tissue disorders · Congenital heart defects · Coronary artery disease · Pregnancy · Post-partum

Introduction

While pregnancy is associated with cardiovascular physiological adaptations, including increased cardiac output, blood pressure, and heart rate (Regitz-Zagrosek et al. 2014), cardiovascular disease may be unmasked during both this period and the peripartum phase. Emerging experience has shown, in many cases, women who face cardiac decompensation during pregnancy carry a previously unknown genetic predisposition to

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cardiovascular disease. Genetic counseling, testing, and family history analysis make it possible to identify them and proactively manage their cardiovascular risk.

The conditions reviewed here have been selected for having a genetic etiology and for being frequent referral indications in cardiogenetics clinics. Some of these conditions can also be a primary feature of a genetic syndrome: channelopathies (Ackerman et al. 2013), cardiomyopathies (Teekakirikul et al. 2013), aortopathies (El-Hamamsy and Yacoub 2009), connective tissue disorders (Beighton et al. 1998), familial hypercholesterolemia (Khoo 2015), and congenital heart disease (notably, Tetralogy of Fallot, bicuspid aortic valve, and coarctation of the aorta). Coronary artery disease (CAD), a common cardiovascular condition of multifactorial etiology, which, in our experience, is frequently reported during family history, is also included. The key clinical and genetic features of these conditions are provided in Table 1.

During pregnancy and the post-partum period, the abovementioned conditions may present with arrhythmia, conduction system disease, congestive heart failure, myocardial infarction, stroke, thrombosis, vascular aneurysm/dissection/rupture, and/or sudden cardiac death. Most of these conditions can be present in the absence of overt symptoms and thus often depend on echocardiography or other cardiac imaging for diagnosis. Unfortunately, they may first come to attention after a catastrophic event, such as sudden cardiac death or aortic dissection.

Perinatologists, cardiologists, and genetic health providers have long worked together to provide perinatal care to affected women. More recently, cardiovascular genetics has developed as a subspecialty providing multi-disciplinary care with the goal of identifying at-risk individuals. The practice model may involve a genetic counselor (and possibly a medical geneticist) embedded in an outpatient cardiology service. Referral patterns may not necessarily reflect the prevalence of a condition (Table 1), but rather recognition, either through personal experience or long-standing literature, of the value of a genetic evaluation for a specific phenotype. Thus, in our experience, referrals for Marfan syndrome, hypertrophic cardiomyopathy (HCM), and Long QT syndrome are relatively more frequent in cardiogenetics.

While the European Society of Cardiology has published management guidelines for cardiovascular conditions in pregnancy (Regitz-Zagrosek et al. 2011), there are no evidence-based guidelines for surveillance of unaffected, at-risk women based on their genotype or family history. To begin addressing this issue, this paper provides expert opinion about the identification and surveillance of women whose symptoms, family history, or predictive genetic testing results indicate an increased risk for developing new onset disease during pregnancy. We provide general genetic evaluation, counseling, and management principles while highlighting disorder-specific information in the accompanying tables. To provide context, we first provide an overview of management as well as general delivery and post-partum considerations for women with heart disease. We then share our approach for a genetic evaluation and counseling for affected women, followed by guidance on how to identify at-risk women. This document also includes expert-based surveillance considerations during pregnancy and the post-partum period, based on our collective clinical experience at various cardiovascular genetics centers in the United States. Finally, we review psychosocial issues that inform how to support patient-centered decisions in this patient population. We propose that a multidisciplinary approach including cardiology, maternal fetal medicine, and genetic counseling best serves this patient population.

Affected Women: Impact on Pregnancy and Management Overview

Pregnancy causes a number of alterations in the cardiovascular system that can result in significant morbidity and even mortality in women affected with heart disease. Heart disease can be asymptomatic; thus an affected woman may have latent or symptomatic disease. In collaboration with cardiologists and high-risk obstetricians, genetic counselors working with affected women assist in the genetic evaluation while providing emotional support. While the medical management of pregnant women with heart disease is the primary responsibility of cardiologists and maternal-fetal medicine physicians, genetic counselors who are members of the healthcare team should be knowledgeable of basic principles guiding the clinical care of this patient group.

Management

Affected women (including those with asymptomatic disease) contemplating pregnancy should have a comprehensive evaluation by a cardiologist, prior to becoming pregnant, whenever possible. Genetic counselors should be able to identify these women and facilitate a cardiovascular genetics referral. The cardiovascular genetic conditions discussed in this section are shown in Table 1. Both the underlying cardiac abnormality and current clinical status are equally important. Risk stratification is a principal goal, and scoring systems, such as the CARPREG score, exist to risk-stratify patients (Lu et al. 2015). Systolic dysfunction can lead to poor maternal outcomes, with a greater than 20% risk of major adverse cardiac events (MACE) during pregnancy for patients with symptomatic heart failure (Siu et al. 2001). Additional concerns include presence of symptoms (New York Heart Association functional class II or higher) (Dolgin 1994), as well as cyanosis, aortic aneurysm, and unstable arrhythmias.

In some cases, pregnancy termination or avoidance of pregnancy is appropriate to protect the life of the mother. Many pregnant women are mis-counseled regarding contraindications

Table 1 Clinical and genetic features

Condition	Prevalence[a]	Imaging	ECG	Possible extra-cardiac features	Signs and symptoms	Inheritance	Genetic testing sensitivity[b]	Comments
Cardiomyopathies: ventricular morphology and function abnormalities								
DCM	1/200–1/2500	Left ventricular dilatation, ejection fraction <50%	LVH		Palpitations, thromboembolic disease, conduction system disease, heart failure	AD, AR, XL, mitochondrial	40% (20% VUS)	
HCM	1/500	LVH	LVH, TWI		Dyspnea, palpitations, chest pain, syncope, heart failure	AD, XL	40–60%	Approximately 5% have multiple variants.
ARVC	1/2000–1/5000	Right ventricular dilatation, reduced right ventricular systolic function, reduced left ventricular or biventricular systolic function, regional RV akinesia, dyskinesia, or aneurysm	TWI in precordial leads, ventricular arrhythmias of left bundle morphology	Woolly hair, palmoplantar keratoderma	Palpitations, dizziness, syncope, heart failure	AD, AR	50–60%	
LVNC	1/7000	Non-compaction of the left ventricular myocardium with prominent trabeculations (may be associated with other types of cardiomyopathy or congenital heart disease).			Arrhythmia, thromboembolic disease, heart failure	AD, XL	17–41%	Genetic overlap with DCM and HCM.
RCM	rare	Reduced diastolic function with normal/near-normal wall thickness and systolic function	Atrial fibrillation is extremely common, if patient in sinus rhythm may have abnormal P waves due to left or right atrial enlargement.	Distal skeletal myopathy, lysosomal or glycogen storage disease, hemochromatosis, pseudoxanthoma elasticum	Atrial fibrillation thromboembolic disease heart failure	AD	20%	
Channelopathies: myocardial ion channel defects								
Brugada	1/5000–1/10,000		J elevation, coved ST elevation, camelback pattern		Syncope	AD	20%	Low penetrance, higher prevalence in South Asia.
CPVT	1/10,000		Polymorphic VT		Syncope	AD, AR	60%	*RYR2* associated with hot spot, *de novo* variants, and 80% penetrance.
LQTS	,2500		Prolonged QT, *torsades de pointes,* bradycardia	Sensorineural hearing loss	Palpitations, syncope	AD	75%	Jervell and Lange-Nielsen syndrome (sensorineural

Table 1 (continued)

Condition	Prevalence[a]	Imaging	ECG	Possible extra-cardiac features	Signs and symptoms	Inheritance	Genetic testing sensitivity[b]	Comments
								deafness and prolonged QT interval) when recessive.
Aortopathies: aortic dilation, aneurysm, or dissection, other vessels may be involved	Marfan: 1/5000–10,000; LDS: unknown	Aortic aneurysm/ dissection MVP BAV, PFO, ASD, VSD	If significant aortic stenosis, voltage criteria for LVH.	Syndromic presentation with **Marfan and Loeys-Dietz syndrome**: skeletal: scoliosis, pectus, clubfoot, joint hypermobility; ocular: ectopia lentis, eye muscle disease, retinal detachment, iris flocculi; cutaneous: translucent skin, abnormal scars, livedo reticularis; vascular: other aortic/arterial aneurysms; **Turner syndrome**: short stature, delayed puberty/amenorrhea, pregnancy achieved with assisted reproductive technology.	Palpitations, dizziness, dyspnea, dissection pain	AD	>90% Marfan and LDS syndrome 16–20% isolated TAAD	Germline mosaicism observed. De novo rates: MFS, 25% LDS, 33%
Ehlers-Danlos syndrome: vascular rupture, aortic aneurysm, hypermobility, hyperflexible skin								
Vascular EDS	1/200,000	MVP aortic aneurysm dissection (may be at normal dimensions)		Cutaneous: easy bruising, translucent skin, fragility; Skeletal: joint hypermobility Vascular: other aortic/arterial aneurysms Other: hollow organ rupture	Autonomic dysfunction, dissection, characteristic facial features	AD	>95%	50% *de novo* Somatic and germline mosaicism can occur.
Cardiac valvular EDS	rare	Valvular defects		Cutaneous: skin hyper extensibility, atrophic scarring	Autonomic dysfunction	AR	unknown	rare
Classic EDS	1/20,000	MVP, TVP, aortic aneurysm		Cutaneous: smooth, fragile, hyperextensible, skin, abnormal wound healing, atrophic scars, easy bruising Skeletal: joint hypermobility Vascular: spontaneous rupture of large arteries	Fatigue, muscle cramps, hypotonia, delayed motor development	AD	50%	50% *de novo*
CAD: atherosclerotic plaque buildup in coronary arteries	1/16	Ischemic cardiomyopathy, coronary artery stenosis	ST and T wave changes, Q waves if prior myocardial infarction.		Dyspnea, chest pain, dizziness, heart attack	Multifactorial	N/A	
FH: elevated low density lipoprotein	1/500	Coronary artery stenosis		Homozygous FH with tendon xanthomas	Angina, peripheral vascular disease	Codominant		

Table 1 (continued)

Condition	Prevalence[a]	Imaging	ECG	Possible extra-cardiac features	Signs and symptoms	Inheritance	Genetic testing sensitivity[b]	Comments
cholesterol and premature atherosclerosis								
Congenital heart disease: structural heart defects	Overall: 1/100 Turner: 1/2000–1/5000 22q deletion syndrome: 1/4000 Noonan syndrome: 1/1000–1/2500	TOF, BAV, coarctation of the aorta, others	Right bundle branch block nearly universal after repair of TOF or other conotruncal defects.	Syndromic presentation with **Turner syndrome:** short stature, webbed neck, broad chest, ovarian failure; **22q deletion syndrome**: cleft palate, learning disability, bulbous nose; **Noonan syndrome**: short stature, skeletal anomalies, hypertelorism, prominent forehead, cutaneous lesions.	Rarely presents in pregnancy	Multifactorial, AD	N/A	

Abbreviations (in alphabetical order): AD, autosomal dominant; AR, autosomal recessive; ARVC; arrhythmogenic right ventricular cardiomyopathy; ASD, atrial septal defect; BAV, bicuspid aortic valve; CAD, coronary artery disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EDS, Ehlers-Danlos, syndrome; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; LDS, Loeys-Dietz syndrome; LQTS, Long QT syndrome; LVH, left ventricular hypertrophy; LVNC, left ventricular non-compaction; MFS, Marfan syndrome; MVP, mitral valve prolapse; PFO, patent foramen ovale; RCM, restrictive cardiomyopathy; RV, right ventricular; TAAD, thoracic aortic aneurysm and dissections; TOF, Tetralogy of Fallot; TVP, tricuspid valve prolapse; TWI, T-wave inversion; VSD, ventricular septal defect; VT, ventricular tachycardia; VUS, variant of uncertain significance; XL, X-linked

[a] References for disease prevalence: DCM (Hershberger et al. 2013), HCM, RCM, Brugada syndrome, and LQTS (Ackerman et al. 2011), ARVC (Teekakirikul et al. 2013), LVNC (Elliott et al. 2008), CPVT (Priori et al. 2013), Marfan syndrome (Judge and Dietz 2005), vascular EDS (Pepin et al. 1997–2013), classic EDS (Malfait et al. 2010), CAD (Mozaffarian et al. 2015), FH (Khoo 2015), and congenital heart defects (Cowan and Ware 2015).

[b] Detection rates based on clinical experience and available literature (Ackerman et al. 2011; Loeys et al. 2010; Malfait et al. 1997–2013; Pepin et al. 1997–2013)

of pregnancy and the need for termination because of their cardiovascular disease. However, the recommendation to avoid or terminate a pregnancy should be carefully weighed as it may be valid in some cases. For example, while the presence of advanced heart failure or severe left ventricular outflow tract obstruction are associated with serious risk, good baseline systemic ventricular function and well-controlled arrhythmia disorders are generally compatible with the ability to maintain a healthy pregnancy.

Surveillance

Cardiac surveillance during pregnancy can include a variety of tests (Zlotogora 1998), including electrocardiogram, ambulatory electrocardiogram, such as a Holter monitor, echocardiogram, cardiac magnetic resonance imaging (MRI), and rarely, procedures requiring ionizing radiation. New symptoms of dyspnea or other symptoms that are likely cardiac in origin should prompt investigation with at least an echocardiogram. Radiation should generally be avoided, but if there is a concern for myocardial infarction, coronary angiography should be done promptly. MRI can be safely performed, but gadolinium contrast cannot be administered during pregnancy due to uncertainty regarding the safety to the fetus (Kanal et al. 2013).

Medical Therapy

Medical therapy can help lower risk of MACE during pregnancy. Diuretics are very frequently used for patients with symptomatic heart failure. Treating physicians should be careful to avoid potential teratogens (Table 2). For example, ACE inhibitors, one of the mainstays of treatment for congestive heart failure, are linked to fetal renal agenesis, and should be stopped prior to attempts to conceive, and as soon as possible once pregnancy is detected. Although there is a concern for fetal growth restriction with beta blockers, beta blockers such as carvedilol and metoprolol are frequently used to treat symptoms of heart failure and arrhythmia during pregnancy, and also to suppress malignant arrhythmias in selected cases.

Delivery and the Post-Partum Period

The increased stroke volume, anxiety, and pain during labor may result in cardiac complications. Therefore, for patients with the highest risk lesions, it is advisable to have a planned delivery, availability of a cardiologist and/or electrophysiologist on staff, and to have maternal telemetry monitoring during labor for conditions at higher risk of leading to malignant arrhythmias. The exact timing of delivery will vary from one woman to the next. Whenever possible, the delivery should be delayed to 37 weeks to allow fetal lung maturity. On a case-by-case basis, delivery may need to be induced rather than spontaneous to allow for a more controlled environment to guarantee availability of key personnel to assist with the delivery.

The post-partum period is a high risk time period for complications, especially during the first 48 hours. Notable concerns at this time are the increased risk of thrombosis and stroke, and also increased risk for ventricular arrhythmias. Measures should be taken to reduce risk of thrombosis, including early ambulation, compression devices, or anticoagulation, depending on the individual patient, balancing risk of thrombosis with risk of bleeding.

Specific Management and Delivery Considerations

Specific cardiac problems affecting pregnancy can be separated into three general categories: 1) hemodynamic problems, 2) vascular concerns, and 3) channelopathies.

Hemodynamic Problems: Cardiomyopathies, Congenital Heart Defects, Pulmonary Hypertension

Management

Hemodynamic problems can lead to either volume or pressure overload of a ventricle. This category includes cardiomyopathies (a weakening of the heart muscle), valvular disease, residual shunts (such as an unrepaired atrial septal defect, ASD), coarctation of the aorta, and pulmonary hypertension (PH) (Elkayam and Bitar 2005a, 2005b; Elkayam et al. 2016; Pijuan-Domenech et al. 2015; Sliwa et al. 2016; Wanga et al. 2016).

For most of these conditions, new symptoms do not occur until well into the second trimester, as the circulating plasma volume increases during pregnancy, with a peak around 28–32 weeks of gestation. This increased volume can thus exacerbate the hemodynamic stress of an already overloaded ventricle. When symptomatic, these lesions generally present with symptoms of heart failure, including dyspnea, orthopnea, and leg swelling. It is very concerning if symptoms of heart failure present in the first trimester, as these will be expected to progressively worsen, and measures must be taken to correct hemodynamic issues as much as possible. As a general rule, pregnant women tolerate volume overload better than pressure overload, thus regurgitant valvular lesions are generally tolerated better than stenotic valvular lesions (Drenthen et al. 2010; Tsiaras and Poppas 2009). Left-sided stenotic lesions are at the highest risk for poor maternal outcomes. Symptoms of volume overload can usually be relieved effectively with diuretic therapy during pregnancy, whereas pressure overload may require mechanical relief of obstruction (Drenthen et al. 2010; Elkayam et al. 2016; Siu et al. 2001).

Table 2 Selected teratogenic risks[a]

Generic name (brand name)	Fetal Risks	FDA Category[b]	Recommendation during pregnancy	Maternal complications	Breastfeeding	Other
Amiodarone (Cordarone)	Developmental delay, growth retardation, cardiac anomalies, nystagmus, head titubation; hypo/hyper-thyroidism.	D	Only use for refractory severe arrhythmias. If exposure occurs, monitor fetal thyroid size. Thyroid function studies recommended for newborns.		Contraindicated; monitor infant cardiac and thyroid function if taken.	Exposure relevant months prior to and throughout pregnancy.
Atenolol (Tenormin)	IUGR, lower birth/placenta weight, premature birth, hypoglycemia, profound beta blockade.	D	Consider an alternative beta blocker. Observe affected neonates for bradycardia and hypotension for 48 hours postpartum.	Maternal renal function, mean cardiac output, and heart rate increased in 2nd/3rd trimester.	Consider an alternative beta blocker; avoid in preterm, infants <3 months and infants with renal disease; if used, monitor infant for beta blockade.	Exposure relevant in 2nd and 3rd trimesters.
Atorvastatin (Lipitor)	Skeletal abnormalities, central nervous system deficiency, increased fetal and neonatal mortality.	X	Contraindicated based on a few case reports; increased preterm delivery risk.		Contraindicated.	
Digoxin (Lanoxin)		C	Monitor serum during late pregnancy. Recommended for SVT fetal tachycardia and in pregnant women with SVT (Blomstrom-Lundqvist et al. 2003).	Hypokalemia	Not expected to cause adverse effects if breastfeeding is avoided for 2 hours after dose.	
Flecainide	IUFD, SIDS, conjugated hyperbilirubinemia.	C			Adverse effects not expected in infants >2 months; monitor infant for toxicity.	
Furosemide (Lasix)	Hypospadias, sensorineural hearing loss, patent ductus arteriosus in premature infants with respiratory distress syndrome.	C	Monitor fetal growth due to potential for higher birth weights. Relatively safe to use if salt restriction is not sufficient.	Hypovolemia, decreased placental perfusion pressure.	Intense diuresis might decrease lactation; limited data; consider alternatives.	Relevant exposure throughout pregnancy.
Heparin		C	Measure factor Xa weekly.	Heparin-induced thrombocytopenia; osteoporosis.		Low molecular weight heparins preferred. Unfractionated heparin is preferred during the last weeks to avoid delivery-associated bleeding.
Hydralazine (Apresoline)	Lupus-like syndrome, unspecified anomalies; fetal toxicity in 3rd trimester.	C	Use during 3rd trimester reported without adverse effects.	Lupus-like syndrome, maternal oliguria, placental abruption, higher C-section rate, hepatic dysfunction (3rd trimester).		Relevant exposure throughout pregnancy.

Table 2 (continued)

Generic name (brand name)	Fetal Risks	FDA Category[b]	Recommendation during pregnancy	Maternal complications	Breastfeeding	Other
Lisinopril (Zestril)	ACE-inhibitor fetopathy: oligohydramnios, IUGR, renal anomalies, and death.	C - 1st trimester. D - 2nd/3rd trimesters	Avoid.	Lightheadedness, dizziness, angioedema.		Relevant exposure throughout pregnancy. Alternative medications: (chlorothiazide, atenolol, labetalol, others).
Losartan (Cozaar)	Oligohydramnios, renal failure, PDA, hypocalvaria, IUGR, neonatal death, fetal death, fetal renal failure.	D	Discontinue.		No data - alternate preferred; avoid in newborns.	Risks due to 2nd/3rd trimester exposures; 1st trimester exposure risks unclear.
Metoprolol (Lopressor)	Associated with beta-blockade (neonatal bradycardia or hypotension, respiratory depression), hypoglycemia. Propanolol – IUGR.	C	For HCM, women continue with treatment during pregnancy. Lower risk with labetalol, propranolol, metoprolol. Exposed neonates should be observed during the first 24–48 hours after birth for bradycardia.		Effects not expected to be significant unless hepatic function is diminished.	
Niacin/nicotinic acid (B-3-50)	Unknown. Can cross the placenta.	C			Known to enter breast milk; decide on a case by case basis.	Dosage effect: upper limit during pregnancy =35 mg/d.
Nitroprusside (Nitropress)	Unknown. Potential for cyanide toxicity.	C	Avoid. Monitor maternal serum pH, plasma cyanide, thiocyanate, and methemoglobin levels.		Avoid.	
Spironolactone (Aldactone)	Can cross the placenta. Potential feminization of male fetus.	C	Contraindicated except for patients with cardiovascular disorders.		Could cause gynecomastia.	
Verapamil (Calan/Isoptin)	Small increase in fetal loss rate with 1st trimester exposure. AV block, hypoperfusion and hypotension risk with 2nd/3rd trimester exposure.	C			Compatible.	
Warfarin (Coumadin)	Skeletal and CNS abnormalities, spontaneous abortion, stillbirth, and neonatal death.	X (D -women with mechanical heart valves)	Avoid, especially in the first trimester.		Compatible.	Alternative medication: heparin.

Abbreviations (in alphabetical order): AV, atrioventricular; CNS, central nervous system; IUFD, intrauterine fetal demise; IUGR, intrauterine growth retardation; HCM, hypertrophic cardiomyopathy; PDA, patent ductus arteriosus; SIDS, sudden infant death syndrome; SVT, supraventricular tachycardia

[a] References: (Briggs 2011; Reprotox)

[b] C- Adverse effect shown in animal studies; no adequate studies in humans, but potential benefits may outweigh risks; D- Positive evidence of human fetal risk, but potential benefits may outweigh risks; X- Studies have demonstrated fetal abnormalities and risk; risks outweigh potential benefits.

Mechanical valves present a unique challenge, given that anticoagulation cannot safely be stopped without placing the mother at risk of thrombosis, but warfarin, the standard treatment, is teratogenic in early pregnancy. As a result, these women are usually managed with low-molecular weight heparin during certain times of their pregnancy. Women with severe PH are also at high risk, with mortality of 28% (Bedard et al. 2009). If there is uncertainty to the cause or the severity of PH, cardiac catheterization, despite risks, may be necessary to determine if it is safe to proceed with the pregnancy. PH due to increased left-to-right shunting by a large ASD may be treatable with device closure of the ASD.

Ideally, valvular disease, shunts, and coarctation of the aorta will be addressed and corrected prior to pregnancy. Unfortunately, in some cases, women are not aware they have these problems until after they become pregnant. It is fairly common, for example, for an atrial septal defect to be diagnosed for the first time during a pregnancy (Uebing et al. 2006; Webb and Gatzoulis 2006). On a case-by-case basis, many of these defects can be palliated or repaired percutaneously during pregnancy if a woman develops significant symptoms and/or imaging evidence of significant cardiac stress. Open-heart surgery will rarely be offered during pregnancy; given the high expected rate of fetal loss due to cardiopulmonary bypass, termination is generally considered if a woman needs open-heart surgery to save her own life.

Delivery

For most women, vaginal delivery is preferred, but for those with systolic dysfunction or significant valvular disease, it is advised that labor be assisted with vacuum or forceps (Elkayam et al. 2016; Uebing et al. 2006). Women with hemodynamic lesions may develop ventricular tachycardia during labor (Nakagawa et al. 2004). Telemetry is generally recommended during delivery and for 1–2 days postpartum for those at higher risk. Patients with residual shunts should be protected from air embolism by placement of specialized filters in their intravenous lines (Bendszus et al. 2004; Wilkins and Unverdorben 2012).

Vascular Concerns: Aortopathies

Management

In patients with vascular abnormalities such as aortic aneurysms, there are usually no symptoms at all, but rather the potential for a catastrophic outcome such as an aortic dissection or rupture, thus monitoring involves periodic imaging, rather than a reliance on symptoms (Wanga et al. 2016).

Beta blockers are frequently used to prevent aortic dilation during pregnancy in Marfan syndrome and other aortopathies (Lind and Wallenburg 2001; Meijboom et al. 2005; Omnes et al. 2013). Although atenolol has been studied the most at prevention of aortic dilation in Marfan syndrome, other beta blockers are preferred in pregnancy, as atenolol is more frequently associated with intrauterine growth restriction (Tanaka et al. 2016).

Delivery

The additional hemodynamic stress of pregnancy, labor, and delivery may increase the risk of aortic complications, thus steps to avoid these complications, such as serial imaging of the aorta, alteration of delivery method, or delivering at an earlier gestation age, may be needed. An aortic aneurysm >4 cm is a major indication for cesarean section, as this may predispose a woman to a potentially fatal aortic dissection (Immer et al. 2003; Yuan 2013).

Vascular concerns in pregnancy also include the potential for spontaneous coronary artery dissection. Spontaneous coronary artery dissection (SCAD) is a rare problem with no known genetic cause identified to date. However, familial disease has been documented and can be associated with an inherited syndrome, suggesting that if an at-risk family member of a known individual affected with SCAD presents with symptoms of acute coronary syndrome, healthcare providers should consider cardiac evaluation (Goel et al. 2015; Nizamuddin et al. 2015). Given that the molecular basis of SCAD is still evolving, it is beyond the scope of this review.

Channelopathies

Management

Women with inherited arrhythmia syndromes may be asymptomatic prior to pregnancy. In inherited arrhythmias, the increased volume during pregnancy has been reported frequently to unmask disease in at-risk women, and also to increase arrhythmias in already affected women (Van Tintelen et al. 2014). In previously unaffected women, this may bring urgent decisions regarding medications, some of which can be teratogenic (Table 2), or if needed, implantation of an internal cardioverter defibrillator (ICD) (Danielsson et al. 2001; Ferrero et al. 2004; Joglar and Page 2014).

Patients with channelopathies might present with palpitations, but in certain conditions the first symptom could be a sudden death, and appropriate risk stratification, including placing an ICD, may be appropriate, to prevent a fatal outcome, with the risk depending on the precise mutation. ICD implantation, however, may be performed in pregnant women after the first trimester using minimal fluoroscopy after careful

discussion of risks and benefits with the patient (Regitz-Zagrosek et al. 2011). Implementation of a wearable external defibrillator may be another alternative.

Women with inherited channelopathies, and to some degree, cardiomyopathies, may be managed with both anti-arrhythmic medication and ICDs. For most women, evidence supports remaining on anti-arrhythmic medication during pregnancy and delivery as long as it is a class C medication or higher (Van Tintelen et al. 2014). Beta blockers are generally well tolerated, with metoprolol being preferable to atenolol for arrhythmias during pregnancy (Table 2). It is optimal for women to be stable without frequent arrhythmias prior to delivery. In patients who already have received a pacemaker or ICD, this information may be obtained from interrogation of their device, although 24 hour Holter monitoring at 7 months gestation is also recommended at several large centers (Bauce et al. 2006; Chandra et al. 1991).

Delivery

Although normal elevation in heart rate is expected during delivery, the increased sympathetic tone due to the pain and anxiety of labor may increase risk of malignant arrhythmia (Ekholm et al. 1994; Gowda et al. 2003). As with women with hemodynamic lesions, women with channelopathies may develop ventricular tachycardia during labor, and thus telemetry during delivery and for 1–2 days postpartum may be recommended for those at higher risk. In women with a prior history of ICD shock, consideration may be given to disable the device during delivery. In women who are treated and stable prior to delivery, it is rare to develop sustained hemodynamically unstable arrhythmias during delivery. It is critical that women requiring antiarrhythmic therapy remain medicated (avoiding teratogenic drugs) throughout the post-partum period.

Genetic Counseling for Affected Women

Women with a cardiovascular genetic condition should be offered cardiogenetic counseling, which consists of clinical assessment, family history, evaluation of genetic testing options, and psychosocial support. Women with congenital heart disease, aortopathy or a connective tissue disorder should also be evaluated by a medical geneticist to rule out syndromic disease. Preconception counseling is preferred.

Preconception Counseling

Preconception counseling is supported by guidelines for management of women with cardiovascular disease (Regitz-Zagrosek et al. 2011). Preconception counseling may also identify at-risk women based on their family history, genotype, or symptoms. During preconception counseling, risks can be discussed and considered with ample time. For instance, performing exercise stress tests on women who are at risk for certain inherited cardiovascular diseases and contemplating pregnancy can help assess their heart's response to the physiological stress of pregnancy and labor. Decisions affecting a future pregnancy can also be made more comfortably. A primary concern addressed in preconception counseling is risk reduction by identification of teratogenic medications and the opportunity to assess the efficacy of alternative medications (Table 2). The preconception period would also allow for family genetic studies, including screening and segregation if a variant of uncertain significance is identified. During preconception counseling, preimplantation genetic diagnosis (PGD), which has been reported for vascular EDS (Bergeron et al. 2014) and other cardiovascular genetic disorders, may be considered (Kuliev et al. 2012).

Family History

Most cardiovascular genetic conditions are inherited in a Mendelian autosomal dominant (AD) pattern, as shown in Table 1 (Morales et al. 2008). AD de novo variants can also result in simplex pedigrees, as may be the case for 50% of *COL3A1*-Ehlers-Danlos syndrome (EDS; Pepin et al. 1997–2013) and 40% of *RYR2*-catecholaminergic polymorphic ventricular tachycardia (CPVT;(Napolitano et al. 2004–2016; Postma et al. 2005). Other patterns of inheritance may be observed. Rare metabolic storage conditions that mimic hypertrophic cardiomyopathy (HCM) are X-linked (Fabry and Danon disease), where the burden of disease is normally greater in males due to their hemizygous state. Autosomal recessive (AR) inheritance can be observed in arrhythmogenic right ventricular cardiomyopathy (ARVC), *CASQ*-CPVT, and Jervell and Lange-Nielsen syndrome caused by *KCNE1* and *KCNQ1* variants. Other conditions, such as CAD (linked to the 9p21 locus) and congenital heart disease, are usually multifactorial, sometimes with non-Mendelian familial aggregation. A pattern of inheritance is best appreciated in a three-generation pedigree format; however, de novo and recessive variants, age-related and reduced penetrance, as well as variable expressivity, can lead to a seemingly negative family history. Therefore, it is these authors' opinion that referral to a cardiovascular genetics consult should be based on the phenotype, and not only on the presence of a family history.

Genetic Risk Assessment

First-degree relatives of individuals affected with an AD condition are at 50% risk, as are the offspring of individuals with a de novo genetic condition. Some cardiomyopathies present with digenic or oligogenic inheritance, and in the case of multiple variants in unlinked genes, the risk to offspring is 50%

for each variant. AR cardiovascular disease is rare. Therefore, the recurrence risk for children of an affected woman with an AR condition is considered low outside of a consanguineous relationship. For isolated congenital heart disease in the absence of a family history, the empirically-based recurrence risk is 5%, but it becomes up to 50% in the presence of an AD inherited condition (Gill et al. 2003). The risk to a fetus of a woman with Turner syndrome depends on the type of chromosomal abnormality (Tarani et al. 1998).

The rare possibility of germline mosaicism must always be considered. This phenomenon may become evident when unaffected parents with negative genetic testing have more than one affected child. Thus, if a woman has had an affected child and genetic testing for both parents is negative, a variant may be confined to the germline and recurrence risk would be approximately 3% (Zlotogora 1998).

Genetic Testing

A genetic diagnosis allows for improved counseling regarding recurrence risks and testing options for at-risk relatives. Diagnostic testing for cardiomyopathy, channelopathy, aortopathy, and FH is offered in multi-gene panels. Detection rates for genetic testing vary by condition (Table 1). If the family variant is known, targeted testing (also known as cascade testing) is recommended after genetic counseling. Table 3 presents known genes in which variants have been reported with the conditions reviewed here. No genes or rare variants for heart diseases that manifest exclusively in pregnancy have been reported to date. Locus and allelic heterogeneity are the norm in cardiovascular genetics. While significant genetic overlap exists between the various cardiomyopathies (and to a lesser extent with channelopathies), the aortopathies, vascular EDS and FH are genetically distinct from each other.

While HCM, arrhythmogenic right ventricular cardiomyopathy (ARVC), the channelopathies, the aortopathies, and EDS are established genetic disorders, there is less agreement regarding the proportion of DCM and RCM that may be genetic. However, a non-genetic etiology for DCM and RCM would be unlikely for a young woman in the reproductive age, thus genetic testing is recommended when non-genetic toxicities (drugs, infections) have been ruled out. Similarly, we propose genetic testing for isolated, non-syndromic congenital heart disease (as suggested by Pierpont et al. 2007), with attention to ruling out secondary causes (maternal diabetes, phenylketonuria, teratogenic exposures). Genetic testing for congenital heart defects is also recommended in the setting of suspected syndromic disease (for example, extra cardiac features) or familial congenital heart disease (Chaix et al. 2016). In these cases, chromosomal microarray (CMA) may be performed (may identify 22q11 deletion syndrome in conotruncal congenital heart disease). Karyotype analysis (gold standard for Turner syndrome) is recommended to rule out Turner syndrome variants. While genetic testing is not clinically available for CAD, FH testing may be considered in cases of elevated low density lipoprotein cholesterol with a history of premature atherosclerosis, myocardial infarction, or stroke (Table 4) (Vohnout et al. 2016). Also, a genetic evaluation should be considered for peripartum cardiomyopathy (PPCM), as variants in DCM genes have been identified in these women (Morales et al. 2010; van Spaendonck-Zwarts et al. 2014).

Genetic testing may have prognostic value during pregnancy. For example, missense variants have been associated with severe pregnancy outcomes in vascular EDS (Murray et al. 2014; Pepin et al. 2014). Moreover, postpartum cardiac events may be more common in individuals with *KCNH2* variants, compared to those with *KCNQ1* or *SCN5A* variants (Seth et al. 2007).

A genetic diagnosis in an affected woman may also indicate options for fetal testing. For example, the fetal QT interval can be measured to evaluate for LQTS (Cuneo et al. 2013). In addition, LQTS, CPVT, cardiomyopathies, and aortopathies can have infant and childhood onset, where early diagnosis may guide management. Therefore, prenatal genetic testing may be offered if a genetic diagnosis is known in the family (including a heritable chromosomal rearrangement in Turner syndrome).

Cord blood or blood draw of the newborn child for genetic testing may also be offered at birth if prenatal diagnosis is declined and a woman is known to carry a variant associated with early onset fatal arrhythmias, as sometimes observed in LQTS (Miller et al. 2004; Tester and Ackerman 2005). In these cases, cord blood testing can provide rapid results that inform management in an infant who may be at risk for sudden infant death syndrome (SIDS) due to the presence of LQTS. Lastly, as it is recommended that all women be offered invasive prenatal testing for chromosomal abnormalities regardless of age ("ACOG Practice Bulletin No. 88 2007. Invasive prenatal testing for aneuploidy. American College of Obstetricians and Gynecologists," 2007), adding molecular testing in cases where the family variant is known may be considered.

Identifying Unaffected, At-Risk Women

In our experience, women often have suspicious symptoms, a known genetic variant or relevant family history, but they are unaware of their risk to develop a cardiac condition during pregnancy. Attention to these findings enables identification of women with heart disease, including those with an asymptomatic phenotype that may evolve into symptomatic disease during pregnancy (Table 4). For example, although no controlled studies show that having a pathogenic variant triggers pregnancy onset of cardiac disease, women who first present with PPCM have retrospectively been found to carry DCM-causing variants

Table 3 Relevant genes for cardiovascular genetic conditions in pregnancy[a]

	DCM	HCM	ARVC	LVNC	RCM	Brugada	CPVT	Long QT	TAAD	EDS	EDS, classic	EDS	CAD	FH	Congenital heart disease
No current role for genetic testing													•		
ACTA2									•						
ACTC (ACTC1)		•		•	•										
ACTN2	•														
AKAP9								•							
ANK2								•							
APOB														•	
CACNA1C								•							
CASQ2							•								
CAV3								•							
COL3A1									•	•					
COL5A1											•				
COL5A2											•				
DES					•										
DSC2	•		•												
DSG2	•		•												
DSP	•		•												
FBN1									•						
FLNA									•						•
GATA4															•
JUP			•												
KCNE1								•							
KCNE2								•							
KCNH2								•							
KCNJ2								•							
KCNQ1								•							
LAMA4	•														
LDB3 (ZASP)	•			•											
LDLR														•	
LDLRAP1														•	
LMNA	•		•												
MYBPC3	•	•		•											
MYH6	•														
MYH7	•	•		•	•										
MYL2		•			•										
MYL3					•										
NKX2.5				•											•
NOTCH1									•						•
MYPN	•				•										
PCSK9														•	
PKP2			•												
PLN			•												
RBM20	•														
RYR2							•								
SCN1B						•									
SCN4B								•							
SCN5A	•		•			•		•							

Table 3 (continued)

	DCM	HCM	ARVC	LVNC	RCM	Brugada	CPVT	Long QT	TAAD	EDS	EDS, classic	EDS	CAD	FH	Congenital heart disease
SMAD3									•						
SNTA1								•							
TBX1															•
TBX5															•
TCAP	•														
TGFB2									•						
TGFB3									•						
TGFBR1									•						
TGFBR2									•						
TMEM43			•						•						
TMPO	•														
TNNI3		•		•	•										
TNNT2	•	•		•	•										
TNXB												•			
TPM1		•		•	•										
TTN	•														
VCL	•														

[a] References: GeneTests medical genetics information resource

(Morales et al. 2010; van Spaendonck-Zwarts et al. 2014). These women should be referred to cardiovascular genetics centers to establish a diagnosis and determine indication for genetic testing. These centers may also have the referral systems in place to ensure comprehensive care.

While it can be difficult to distinguish cardiac symptoms from those experienced during normal pregnancy, the concern is higher when multiple symptoms are present, or with dyspnea and syncope. In terms of family history, we suggest a genetic consult for women reporting a family history of sudden cardiac death under age 60 in a first or second degree relative. Additional concerning findings are shown in Table 4.

Managing risks associated with PPCM has been discussed for some time, and a validated PPCM self-test has been developed for early recognition of heart failure symptoms (Fett 2011), though now potential risks are also recognized for women at risk for other cardiomyopathies. Unaffected variant carriers, as well as those with a family history of cardiomyopathy, early onset-arrhythmia, heart failure, or skeletal myopathy should be referred for a cardiac evaluation.

Women at risk for channelopathies may have their first event while pregnant or in the peripartum period. At-risk women may be genotype positive for a variant predisposing to Brugada, CPVT, or LQTS, or have a family history of syncope, unexplained death or drowning, or SIDS. High-risk symptoms include palpitations, presyncope, and syncope, especially during high adrenaline situations or exercise for CPVT or LQTS (Gollob et al. 2011). These symptoms should also initiate a prompt referral to an electrophysiologist.

Aortopathies, especially Marfan syndrome and other connective tissue disorders such as vascular EDS, present significant risks because aortic enlargement may progress in pregnancy (Bons and Roos-Hesselink 2016). Women at risk for connective tissue disorders, which can sometimes have aortic involvement, may have joint hypermobility or tissue fragility. Concerning symptoms for dissection or valvular disease in at-risk women include severe chest pain, dyspnea, fatigue, swollen feet and ankles, as well as stomach, back, head or neck pain.

CAD is one of the most common causes of death in women today. Pregnant women at elevated risk for CAD may have a family history of CAD in men below age 50 or in women below age 60. They may also have FH, which indicates lipid or molecular testing (Vohnout et al. 2016).

In the case of congenital heart disease, an echocardiogram is recommended for all first degree relatives of an individual with bicuspid aortic valve (BAV), and many make this recommendation in cases with left ventricular outflow tract malformation (such as aortic stenosis, coarctation of the aorta, and hypoplastic left heart syndrome) (Kerstjens-Frederikse et al. 2011; Panayotova et al. 2013). A prior history of BAV, coarctation, and/or aortic aneurysm is also associated with an increased risk for aortic dissection and rupture in women with Turner syndrome. In the past, these women rarely achieved a pregnancy, though now with assisted reproductive technologies, this is

increasingly common. This new reproductive potential suggests need for cardiac screening in women with a first-degree relative with a congenital heart defect who are contemplating a pregnancy.

Cardiac Surveillance for Unaffected At-Risk Women

While managing women with a clear-cut genetic cardiovascular disease may be an obvious point-of-care, management guidance is less clear for women who, based on absence of symptoms are presumed unaffected. It is important to closely monitor throughout the pregnancy and post-partum period in consultation with a cardiologist or electrophysiologist. Surveillance may vary depending on the condition, family history, and genetic testing. Table 5 presents cardiac screening considerations for at-risk women.

In some cases, a specific genetic diagnosis confirming the presence of a pathogenic or likely pathogenic variant may have additional implications for management (Rashba et al. 1998). For instance, asymptomatic women with a first-degree relative confirmed to have QT prolongation may be offered beta blocking agents. Unaffected women who are known to carry a pathogenic or likely pathogenic *SCN5A* variant (reported with ARVC, DCM, LQTS, and Brugada) may also benefit from echocardiography screening. For women at risk for aortopathy, knowing the specific genetic basis can inform vascular imaging.

If surveillance identifies a phenotype, fetal screening should be considered. While fetal diagnosis of HCM and ARVC is rare (Groeneweg et al. 2015; Weber et al. 2014), in comparison, cases of fetal DCM and LVNC are more frequently reported (Jacobs et al. 2014; Pedra et al. 2002). Thus, assessment of structural cardiac changes may be considered in fetuses at risk for DCM and LVNC, particularly if there is a family history of childhood onset disease. Fetal echocardiogram should also be performed if a parent has congenital heart disease (Kerstjens-Frederikse et al. 2011; Panayotova et al. 2013). This is particularly important for BAV, given rare risk of severe left-sided heart defects. Fetuses at risk for congenital heart disease should also be monitored for intrauterine growth restriction. Arrhythmia may be present in a fetus affected with LQTS. Although screening recommendations have not been established, prenatal diagnosis of LQTS using non-invasive fetal ECG has been documented (Cuneo et al. 2013).

Psychosocial Issues

Several studies have shown that individuals with cardiogenetic disorders have elevated anxiety and psychological distress (Cox et al. 1997; Morgan et al. 2008; Poole and Morgan 2006). This underlying distress can be attributed to several factors: risk of sudden death, concern about the impact of the disease on themselves, and worry about impact of risk on other family members (Burkett and Hershberger 2005; Hidayatallah

Table 4 Findings indicating increased risk for a cardiovascular genetic disorder in pregnancy

Finding	Suspected disorder(s)
Patient signs and symptoms	
Shortness of breath, dyspnea upon exertion, orthopnea, severe peripheral edema	Cardiomyopathy, aortopathy
Syncope, presyncope, palpitations	Channelopathy, cardiomyopathy with arrhythmia.
Severe chest pain, stomach pain, back, head or neck	Aortopathy
Tissue fragility joint hypermobility	Connective tissue disorders
Family history	
Known or suspected cardiovascular genetic disorder in a first or second degree relative	All
Sudden death under age 60	All
Early onset-arrhythmia or heart failure, skeletal myopathy	Cardiomyopathy
Syncope, unexplained death or drowning, sudden infant death syndrome	Channelopathy, cardiomyopathy with arrhythmia
Aortic/arterial aneurysms/dissections	Aortopathy, connective tissue disorders
Myocardial infarction, coronary artery disease (men <50 yo; women <60 yo) LDL >190 (adult), >160 (children) mg/dL	Coronary artery disease, familial hypercholesterolemia
Child with congenital heart disease , or ≥2 first or second degree relatives with left sided or conotruncal defect	Congenital heart disease
Genetic testing results	
Pathogenic or likely pathogenic variant	All

Table 5 Preliminary cardiac surveillance considerations for unaffected at-risk women[a]

Condition	Cardiovascular risks for affected women	Surveillance	Intervals	Surveillance for fetus
Cardiomyopathies	DCM: LVHF HCM: LVOT obstruction ARVC: VT, RVHF LVNC: LV HF, thromboembolism RCM: pulmonary edema	Closely monitor for signs and symptoms. ECG, echocardiogram, and Holter monitoring	Baseline[b], repeat during pregnancy (7 months) and post-partum (3 months)	Fetal echocardiogram if at risk for LVNC or family history of infant onset DCM.
Channelopathy	Brugada, CPVT, LQTS: lethal arrhythmia CPVT: arrhythmia	ECG, referral to electrophysiology	Baseline, repeat during pregnancy (7 months) and post-partum (3 months)	Fetal ECG
Aortopathies and other connective tissue conditions	MFS, LDS, TAAD, BAV/ aneurysm, CTDs: aortic dissection, aortic and mitral insufficiency LDS: hemorrhaging, arterial dissection Vascular EDS: peripartum hemorrhage, arterial rupture, aortic enlargement	Echocardiography to assess the aorta-ophthalmology consult, vascular imaging of other arteries may be considered for LDS or vascular EDS	Prior to pregnancy. May repeat imaging at 1–3 month intervals extending up to 6 months post-partum. Ophthalmology at baseline, then as indicated.	Fetal echo may be performed for BAV, because of rare risk of severe left-sided heart defects
FH	MI	Closely monitor cholesterol	Throughout pregnancy and 6 weeks post-partum (levels return to baseline)	
CAD	MI, coronary artery dissection, and thrombosis near delivery and post-partum	ECG if symptomatic		

Abbreviations (in alphabetical order): ARVC, arrhythmogenic right ventricular cardiomyopathy; BAV, bicuspid aortic valve; CAD, coronary artery disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; CTD, connective tissue disorders; DCM, dilated cardiomyopathy; EDS, Ehlers-Danlos syndrome; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; LDS, Loeys-Dietz syndrome; LVHF left ventricular heart failure; LVNC, left ventricular non compaction; LQTS, long QT syndrome; MFS, Marfan syndrome; RCM, restrictive cardiomyopathy; RVHF, right ventricular heart failure; TAAD, thoracic aortic aneurysm and dissection; VT, ventricular tachycardia

[a] At-risk women refers to phenotype negative women with a pathogenic or likely pathogenic variant or at 50% risk for a cardiovascular genetic condition based on family history

[b] Baseline evaluation should be performed in the preconception period, or as close to the beginning of pregnancy as possible

et al. 2014). Pregnancy, however, brings to the forefront the pregnant woman's anxiety and guilt about passing the disease on to her offspring, concern about adverse outcome for the pregnancy, fear of her own death during or post-pregnancy, uncertainty around risk for subsequent pregnancies, as well as feelings of isolation (Hess and Weinland 2012; Hess et al. 2010; Wang 2009). A common psychosocial concern that arises during genetic counseling sessions with an affected individual is the fear of transmitting the disease to one's child.

Progression of disease, safety for themselves, and the risk of maternal death are cited as sentinel concerns. There is a great deal of literature addressing the clinical and medical management factors that influence adverse versus favorable outcomes of maternal cardiovascular disease during pregnancy (Elkayam et al. 2001; Fett et al. 2015; Hameed et al. 2001; Hassan et al. 2015; Lima et al. 2015; Palmquist et al. 2009). It is also known that mothers diagnosed with a known genetic condition such as EDS experience fear. These women need ongoing psychological support to allow them to process their fears to facilitate compliance with medical management recommendations (Palmer 2006). This is of particular importance in women who may experience an unplanned pregnancy even at the express recommendations to avoid pregnancy due to their cardiac disease.

Uncertainty about the implications of cardiac disease on subsequent pregnancies is a common concern. Additionally, despite potential life-threatening risk, the desire for children is pervasive. A study analyzing 247 postings to an online support group for women with PPCM found that concerns about future pregnancies were mentioned 102 times (Hess and Weinland 2012). Another study reported that women used support groups to help identify other women with cardiovascular disease who became pregnant again (Hess et al. 2010). Thus, it is critical to make resources available to help process their concerns as they weigh the risks and benefits of future pregnancies.

Given the risk for pregnancy and maternal complications, a pregnant woman's emotions are complicated by fear over a possible loss and self-blame for putting the pregnancy at risk

due to her own illness. This self-blame can occur even when maternal disease is not diagnosed until pregnancy.

Another concern that arises during genetic counseling sessions, once a heritable disorder is identified in a woman, is the fear of transmitting the disease to their child (Helbig et al. 2010; Klitzman et al. 2007). For those pregnant women who present to genetics with a known hereditary cardiac condition for which the disease-causing mutation is identified, the option of prenatal diagnosis would be available. It is well-documented that having to make a decision to undergo invasive prenatal testing can lead to increased maternal anxiety in pregnancy (Allison et al. 2011; Grobstein 1979; Weil 2000). In addition, prenatal diagnostic testing outcomes can also have psychological repercussions on the pregnant female. A negative prenatal diagnostic genetic test indicating the fetus did not inherit the condition from the mother, may allay the woman's fears of passing the condition on to the child. In the case of a positive prenatal genetic test result, at a minimum two possibilities could occur. A prenatal diagnostic test indicating the fetus is affected may help the mother-to-be, as it provides time before delivery to psychologically adjust to the diagnosis in her child and make preparations for delivery (Rychik et al. 2013). A positive result, however, may also lead to additional distress, because it prompts discussions regarding whether to continue or terminate the pregnancy and because in the case of continuation of pregnancy it leads to knowledge that the future child is at risk for the genetic disorder.

For those women who are diagnosed during a pregnancy or post-partum with a possible hereditary cardiac condition, there is the additional issue of having to first confirm a molecular cause in themselves. Healthcare providers caring for pregnant and post-partum women with a presumed hereditary cardiac disorder need to be cognizant of the client's stress due to the clinical situation. In fact, one could argue that if there is no immediate risk to the woman or to the child, it may be in their best interest to defer a genetic work-up until several months after a child's birth. This would allow for some normalcy to the pregnancy course and facilitate maternal-child bonding post-delivery.

Given the mental and emotional risks involved, it is, therefore, critical that management for pregnant women with cardiogenetic conditions include psychological risk assessment and supportive counseling. This is of particular importance as there are some preliminary data that suggest women diagnosed with peripartum cardiovascular disease do not feel they received appropriate psychosocial support (Wang 2009). There have been several publications calling for the inclusion of psychologists in the treatment and management of at-risk cardiogenetic clients (Hidayatallah et al. 2014; Webb and Williams 2001; Higgins et al. 2007). We propose that genetic counselors also fill a critical role providing psychological support to affected and at-risk women with cardiogenetic disorders (Ingles et al. 2008; Bieskeker 2001). Genetic counselors can provide: education to facilitate decision-making about genetic testing and pregnancy management; short-term counseling to assist women in adjusting to their risk status; and information about reputable advocacy organizations or patient-to-patient connections so women can obtain peer support. In addition, genetic counselors can facilitate referrals to psychotherapists for more in-depth mental health interventions necessary for coping with perceived and actual risks.

Conclusion

Cardiac decompensation during pregnancy can be an issue for both affected and at-risk women, leading to serious complications. Establishing an early diagnosis may be difficult, as symptoms may be dismissed as pregnancy-related physiological changes. A family history should be obtained in all pregnant women who seek medical care. Attention to cardiovascular findings can identify at-risk women, indicating need for cardiology and high-risk obstetrical care, as well as genetic counseling. Because of the many risks and time constraints involved during pregnancy, preconception counseling is preferred. Research relevant to surveillance of unaffected at-risk women should be further developed. Conducting research in pregnant women, considered a vulnerable population, is, however, difficult. Regulatory and patient-related issues are cited as challenges hampering progress (Naqvi 2014).

Collaboration between cardiologists and genetic specialists can be useful in establishing a clear phenotype and a genetic testing strategy. Discussing risks associated with misuse of genetic risk information (and available legal protections such as the Genetics Information Non-discrimination Act; GINA), and interpreting variants of uncertain significance also require expertise. Genetics professionals are thus an important part of clinical care for women with, or at risk for, a cardiogenetic condition. A map showing geographical locations of cardiovascular genetic counselors (many of whom work closely with cardiogeneticists and cardiologists with expertise in genetics) is available at: http://goo.gl/maps/NK8z.

Compliance with Ethical Standards

Conflict of Interest Ana Morales, MS, CGC - none.
Dawn C. Allain, MS, CGC - none.
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