

Who needs a fetal echocardiogram?

A review of the risks, benefits, and indications for appropriate referral of fetal echocardiography

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Congenital heart disease (CHD) is the most common major birth defect and represents the leading cause of infant death from a congenital anomaly.^{1,2} In high-resource settings, CHD accounts for roughly 4% of all neonatal deaths and 30% to 50% of deaths related to congenital anomalies.^{1,2} The incidence of CHD among live births is 6 to 12 per 1000 and is likely an underestimate given both spontaneous and elective terminations with CHD.^{3,4} Identified risk factors for fetal CHD are broadly placed into 3 categories: maternal factors, fetal factors, and familial risk factors. Considering these risk factors, patients with

increased risk should be considered for fetal echocardiography.⁵ Here, we review the tenets of fetal echocardiography, including the risks, benefits, and the indications for appropriate referral (**Figure 1**).

Fetal echocardiogram

Unlike fetal cardiac screening (ie, a detailed anatomical ultrasound and fetal anomaly screen), fetal echocardiography should be reserved for high-risk populations. Pregnancies at higher than population-based risk for CHD require a comprehensive evaluation of the fetal heart by fetal echocardiography. There are a myriad of national and international guidelines

that standardize the requirements for fetal echocardiography. These guidelines are collated by multiple organizations, including the American Institute of Ultrasound in Medicine, the International Society of Ultrasound in Obstetrics and Gynecology, the American Heart Association, and the Association for European Pediatric Cardiology, among others.⁵⁻⁹ The fetal echocardiogram should include a detailed assessment of fetal situs, cardiac axis, cardiac chambers, great vessels, atrioventricular and semilunar valves, systemic and pulmonary venous connects, cardiac function, and rhythm. The presence of clear guidelines by societies helps standardize the approach to



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evaluation of the fetal heart.

A fetal echocardiogram should generally be performed between 18 and 22 weeks' gestation; however, the exact timing is determined by a multitude of other factors including the timing of risk factor identification and the screening diagnosis that warrants the exam, as well as a variety of relevant resources, including the availability of first trimester echocardiography, financial and logistic considerations, and appointment availability. Frequency and follow-up of echocardiography should be personalized and depend on practice location, available resources, and natural history of disease to optimize postnatal delivery planning. Delivery planning echocardiograms are triaged based on disease progression, modifications of postnatal coordination, and limitations with initial imaging.^{10,11}

Risks and benefits of prenatal screening and diagnosis of CHD

The benefits of prenatal screening revolve around parental and postnatal preparation with a subsequent improvement in neonatal morbidity and mortality. Parental counseling and preparation should not be underestimated. Even if the exact lesion or postnatal plans are not finalized until birth with the postnatal echocardiogram and clinical assessment of the neonate, prenatal detection allows the family to obtain prognostic information prior to birth and to make informed decisions on the pregnancy including expectant management, in utero interventions, and terminations. More so, it allows the family to optimize delivery planning, including the location, timing, and mode of birth to optimize both maternal and neonatal outcomes.

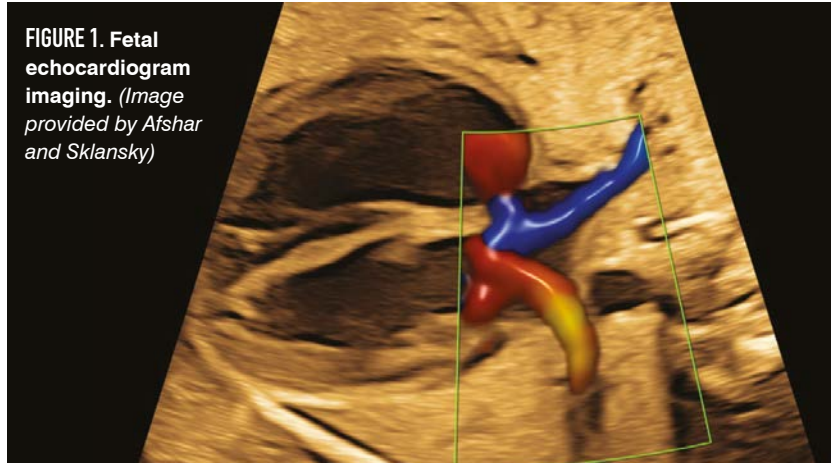


FIGURE 1. Fetal echocardiogram imaging. (Image provided by Afshar and Sklansky)

Prenatal diagnosis of CHD improves neonatal survival.¹² Neonatal morbidity is improved by optimizing and identifying the patients who would require immediate intervention at birth, including prostaglandin administration, transcatheter intervention, and possible pacing.

Opportunities for fetal treatment, specifically transplacental medical therapy for some fetal arrhythmias, are obviously beneficial with earlier diagnosis. Invasive prenatal interventions, such as for severe valvular abnormalities and hypoplastic left heart syndrome, remain mostly under research protocols.

The risks related to performing fetal echocardiography, particularly in the absence of cardiac findings on routine screening, include the potential for familial and parental anxiety, false-positive diagnosis, additional unnecessary testing and interventions, and the undetermined cost-effectiveness and a priori determined risk level. More so, most critical cardiac lesions are not missed in a detailed anatomical evaluation.¹³

Who should get a fetal echocardiogram?

Clinical risk factors for CHD (**Table**)

are positioned into 3 risk categories: familial, maternal, or fetal conditions.^{5,6} It remains a topic of debate what percentage over the baseline prevalence (0.3%-1.2%) necessitates additional screening by fetal echocardiogram. Though we make recommendations based on the evidence, this decision must be applicable to the community being served and include an analysis of the benefit from fetal echocardiography over screening and the sophistication of ultrasound screening (vs fetal echocardiography) at the center that the pregnant patient receives care.

In many areas, the No. 2 reason that most pregnant people are sent for a prenatal fetal echocardiogram is for a suspicion of structural heart disease seen on an obstetrical ultrasound, which results in a diagnosis in around 50% of cases. Risk factors that warrant a fetal echocardiogram are summarized in **Figure 2** and the **Table**.

Maternal factors that warrant a fetal echocardiogram

Both pregestational diabetes and phenylketonuria are metabolic conditions that increase the risk of fetal

Table. Indications for Fetal Echocardiogram

Indication	AHA	AIUM	Our recommendation
Maternal metabolic disease			
Pregestational diabetes	Indicated	Indicated	Indicated
Gestational diabetes diagnosed in first or early second trimester	Consider if HbA _{1c} > 6% in third trimester	Indicated	Consider
Phenylketonuria (periconception phenylalanine level > 10 mg/dL)	Indicated	Indicated	Indicated
Phenylketonuria well controlled (periconception phenylalanine <10 mg/dL)	Not indicated	Not indicated	Not indicated
Phenylketonuria (unknown status)	--	Indicated	Indicated
Maternal systemic lupus erythematosus or Sjögren's syndrome			
SSA or SSA/SSB positive without prior affected fetus	Indicated*	Consider	Indicated
SSA or SSA/SSB positive with prior affected fetus (CHB or neonatal lupus)	Indicated**	Indicated	Indicated
SSA or SSA/SSB positive third-trimester evaluation	Consider	--	Consider
Medication exposures (in first trimester unless otherwise specified)			
Anticonvulsants (carbamazepine)	Consider	Consider	Consider
Lithium	Consider	Consider	Consider
ACE inhibitor	Consider	Consider	Consider
Retinoic acid	Indicated	Indicated	Indicated
SSRIs (other than paroxetine)	Not indicated	Not indicated	Not indicated
Paroxetine	Consider	Consider	Consider
Vitamin K antagonists	Not indicated	Not indicated	Not indicated
NSAID (first trimester)	Consider	--	Consider
NSAID (third trimester)	Indicated ^	--	Consider
Infection			
First-trimester rubella infection	Indicated	Indicated	Indicated
Maternal fever or viral infection with seroconversion only	Not indicated	Not indicated	Not indicated
Fetal myocarditis/pericarditis suspected ^	Indicated	--	Indicated

embryopathy and abnormal cardiac development, specifically related to teratogenicity targeted toward cardiac development. Pregestational diabetes affects nearly 2% of all pregnancies. Pregestational diabetes is associated with a 5-fold increase (3%-5%) in CHD and can affect the fetal heart in several ways.^{14,15} First, the risk of fetal congenital heart disease is markedly increased as glucose works as a teratogen in cardiac development; second, fetal hypertrophic cardiomyopathy may occur even with good glycemic control; and third, studies have shown impaired function of the heart of some infants and fetuses of diabetic pregnancies, which can occur with and without septal hypertrophy. The relative risk (RR) of fetal CHD varies based on the specific cardiac defect, but the RR for single ventricle defects is as high as 18.24.¹⁵⁻¹⁷

All pregestational diabetic pregnancies are associated with an increased risk of CHD, regardless of hemoglobin A_{1c} (HbA_{1c}). In contrast, with pregestational diabetes, third trimester insulin resistance of gestational diabetes does not increase the risk of CHD. Importantly, however, poorly controlled gestational diabetes can be associated with fetal ventricular hypertrophy and the degree of hypertrophy is related to glycemic control.

Maternal phenylketonuria (PKU) presents some risks to the fetus similar to pregestational diabetes. Untreated maternal PKU is associated with adverse pregnancy outcomes, which include CHD, neurodevelopmental delay, microcephaly, and fetal growth restriction. Elevated maternal phenylalanine (> 15 mg/dL) is associated with a 10- to 15-fold

increased risk of CHD. There is a startling 12% risk of fetal CHD if diet control of PKU is not achieved by 10 weeks with no increased risk if phenylalanine levels less than 6 mg/dL before conception. Both maternal diabetes and PKU present examples where prepregnancy optimization of metabolic conditions can improve pregnancy outcomes including risk of fetal CHD.

The association and fetal risk of congenital heart block (CHB) with maternal lupus and Sjögren's syndrome is well known, and the incidence is based on prior history of an affected child and SSA-(anti-Ro) or SSB-(anti-La) positive antibodies, independent of connective tissue disease status. Neonates that have CHB have a 20% mortality rate and 65% of the neonates receive permanent pacing.¹⁸ While the incidence of fetal CHB with a prior affected child and SSA- or SSA/SSB-positive antibodies is 11% to 20%, SSA-or SSA/SSB-positive antibodies with no prior affected children is associated with a 1% to 5% risk, and positivity with hypothyroidism is associated with a 9-fold increase in risk compared with positive antibodies alone. Higher SSA values (> 50 U/mL) correlate with increased fetal risk and that 10% to 15% of SSA-exposed fetuses may also or alternatively develop additional complications. The role of SSB antibodies (alone) in CHB is unclear, and currently no high-level evidence exists to recommend for CHB if SSB positive and SSA negative. In many practice settings, SSA or SSB positivity is treated the same. SSA/SSB IgG antibodies do cross the placenta and the current mechanistic hypothesis, though unproven, is thought to be

Table. Indications for Fetal Echocardiogram Continued			
Indication	AHA	AIUM	Our recommendation
Family history			
First-degree relative with structural cardiac disease (maternal, paternal, prior pregnancy/affected sibling)	Indicated	Indicated	Indicated
Second-degree relative with cardiac disease	Consider	Consider	Consider
Third-degree relative with cardiac disease	Not indicated	Not indicated	Not indicated
First- or second-degree relative with disease of Mendelian inheritance associated with structural cardiac disease	Indicated	Indicated	Indicated
Suspected fetal cardiac abnormality or rhythm disturbance			
Suspected structural cardiac abnormality	Indicated	Indicated	Indicated
Tachycardia [#]	Indicated	Indicated (persistent > 180 bpm)	Indicated
Bradycardia [#] or suspected congenital heart block	Indicated	Indicated (persistent < 120 bpm)	Indicated
Frequent episodes or persistent irregular rhythm	Indicated	Indicated	Indicated
Extracardiac fetal anomalies			
Major fetal extracardiac anomaly	Indicated	Indicated	Indicated
Known or suspected chromosomal abnormality	Indicated	Indicated	Indicated
Abnormality of umbilical cord (ie, SUA)	Consider	Not indicated	Consider
Systemic venous anomaly	Consider	Consider	Consider
Thickened nuchal translucency (NT)			
Increased NT > 3.5 mm	Indicated	Indicated	Indicated
Increased NT 3.0-3.4 mm	Consider	Consider	Consider
Increased NT 3.0-3.4 mm with abnormal ductus venosus	Indicated	--	Indicated

Table. Indications for Fetal Echocardiogram Continued

Indication	AHA	AIUM	Our recommendation
Other maternal or fetal factors			
Monochorionic twins	Indicated	Indicated	Indicated
Hydrops fetalis	Indicated	Indicated	Indicated
In vitro fertilization, including ICSI	Indicated	Indicated	Indicated

AHA, American Heart Association; AIUM, American Institute of Ultrasound in Medicine; ACOG, American College of Obstetricians and Gynecologists; bpm, beats per minute; HbA_{1c}, hemoglobin A_{1c}; SMFM, Society for Maternal-Fetal Medicine; SUA, single umbilical artery; SSRI, selective serotonin reuptake inhibitor; NT, nuchal translucency; ICSI, intracytoplasmic sperm injection.

*Initiate at 16 weeks, then weekly or every other week to 26-28 weeks.

**Initiate at 16 weeks, then weekly to 26-28 weeks.

^Recommendation for exclusion of ductal constriction only, up to daily during exposure.

#Bradycardiac and tachycardia definition different in AIUM vs ACOG/SMFM.

related to an activated inflammatory processing leading to scarring, fibrosis and, permanent myocardial and conducting system damage. CHB is most often identified after 18 weeks' but before 28 weeks' gestation, so monitoring for CHB are via mechanical PR intervals through M-mode or Doppler during this interval is recommended. The elephant in the room (for monitoring for CHB) remains standing. No current data, including steroids, slow or reverse CHB after diagnosis. Current trials are ongoing, including the use of intravenous immunoglobulins and other surveillance protocols.

We recommend if maternal autoantibodies (SSA or SSA/SSB) are identified, a fetal echocardiogram should be performed and serial ultrasound evaluation of growth and assessment of PR-intervals could be offered and coordinated, though this remains controversial considering a lack of intervention. Unaffected neonates should receive a postnatal electrocardiogram and if a neonate has CHB, maternal testing for SSA and SSA/SSB auto-antibodies should be done.

MEDICATION EXPOSURE THAT WARRANTS A FETAL ECHOCARDIOGRAM

The Table demonstrates a summary of medication exposure that would increase risk of CHD to levels that warrant at least consideration of a fetal echocardiogram. Very few medication exposures get to this limit. Notably, most of these recommendations come from retrospective or registry data fraught with bias and our recommendations are based on the available evidence. Maternal benefit of medication exposure must always be balanced against a theoretical risk of transplacental passage and fetal risk. Retinoic acid exposure and first trimester angiotensin-converting enzyme (ACE) inhibitor use warrant a fetal echocardiogram. For retinoic acid, cardiac malformations, specifically, conotruncal defects and aortic arch anomalies have been reported in 8% to 20% of exposed fetuses.¹⁹ First-trimester ACE inhibitor exposure is associated with increased risk for CHD where 2.9% of exposed neonates (vs 0.78% of unexposed neonates)

have CHD with a RR of 3.72.^{20,21} Most reported CHDs in this population are lesions not usually detected prenatally: atrial septal defects (ASDs) and patent ductus arteriosus.

At this time, we do not recommend routine fetal echocardiography for pregnant people with selective serotonin reuptake inhibitor (SSRI) use as there is no increased risk of CHD associated with the use of most SSRIs. The only exception is paroxetine. First-trimester paroxetine exposure is associated with a small increased risk of CHD (odds ratio [OR], 1.72; 95% CI, 1.22-2.42). A study of 10,000 infants with birth defects demonstrated that SSRI use was not associated with increased in risk of CHD (OR, 1.2; 95% CI, 0.9-1.6), though there was a possible increased paroxetine exposure among infants with outflow tract abnormalities (OR, 3.3; 95% CI, 1.3-8.8).²²

Antiseizure medication, specifically carbamazepine, is no longer considered to increase the risk of fetal CHD above baseline. The mood stabilizer lithium also was historically believed to significantly increase the risk of cardiac malformations. Registry studies reported the risk up to 8% in offspring exposure to lithium; however, studies suggest the risk is not as high as initially thought with a RR of 1.1.²³

First-trimester warfarin use greater than 5 mg is teratogenic; however, there is no increased risk of CHD despite the increased risk of other defects.²⁴ Nonsteroidal anti-inflammatory use is common and there is ultrasound evidence (without clinical correlate) of ductal constriction in indomethacin-exposed late-trimester pregnancies.²⁵

MATERNAL INFECTION

Febrile maternal illness has been

associated with increased risk of CHD (OR, 1.8; 95% CI, 1.4-2.4), but not significantly above baseline population risk. As such, the only indication during an infection for a fetal echocardiogram is in the setting of an infection with pericardial effusion/hydrops.²⁶ Otherwise, first-trimester infection with rubella should also prompt a fetal echocardiogram. Congenital rubella syndrome from maternal rubella infection is associated with CHD (pulmonary artery stenosis). The risk of congenital defects is limited in the first 16 weeks (Table). Exposure to or seroconversion from other viral illnesses in pregnancy, including SARS-CoV-2, is not as likely to be associated with cardiac abnormalities. However, fetal pericarditis or myocarditis may be seen in parvovirus, coxsackievirus, adenovirus, or cytomegalovirus, and a fetal echocardiogram is recommended.

IN VITRO FERTILIZATION

A recent area of controversy is related to in vitro fertilization (IVF) pregnancies and the rate of CHD. Many studies report an increased rates of CHD with IVF compared with naturally occurring pregnancies originally reported (1.1%-3.3%), and most CHDs are atrial septal defects (ASDs) and ventricular septal defects (VSDs). The incidence of CHD in pregnancies achieved with IVF without risk factors is not significantly different from baseline population rates (OR, 1.4; 95% CI, 0.9-2.1).²⁷ The Society for Maternal-Fetal Medicine still encourages a fetal echocardiogram in IVF pregnancies regardless of intracytoplasmic sperm injection.²⁸ The cost-effectiveness of routine screening for CHD in pregnancies following IVF has been questioned.²⁹

FIGURE 2. RISK FACTORS FOR FETAL HEART DISEASE

MATERNAL COMORBIDITIES

- Pregestational diabetes
- Phenylketonuria
- SSA or SSA/SSB auto-antibodies
- IVF pregnancy (with ICSI)
- Infection*
- Medication exposure*

FAMILY HISTORY

- First- or second-degree family history of cardiac disease

FETAL CONDITIONS

- Suspected cardiac abnormality
- Cardiac rhythm or rate disturbance
- Major extracardiac anomaly
- Known or suspected chromosomal abnormality
- Increased nuchal translucency
- Monochorionic translucency
- Hydrops fetalis

FETAL CARDIAC FACTORS: STRUCTURE, RATE, AND RHYTHM

An obvious and the most common indication for a referral for fetal echocardiogram is a suspected structural cardiac abnormality, suspected rhythm, or suspected rate abnormality. The diagnostic yield after abnormal screening on an obstetrical ultrasound is significantly better than noncardiac screening indications for fetal echocardiogram. During cardiac screening ultrasounds, the diagnostic yield of fetal CHD that comes from an abnormal 4-chamber view is 40%, the addition of the right and left outflow tracts increases the screen positivity rate to 52%, and incorporating the 3-vessel view with trachea further increases the detection of CHD.^{5,30,31}

As for rhythm abnormalities, fetal bradycardia secondary to CHB is associated with CHD in approximately 50% to 55% of cases, and fetal bradycardia may also be associated with left-sided or polysplenia phenotype forms of heterotaxy. Fetal tachycardia rarely may be associated with CHD but is still an indication for fetal echocardiography as in cases of tachyarrhythmia or bradyarrhythmia, an echocardiogram can assess cardiac structure and function, determine the underlying mechanism of tachycardia or bradycardia, and guide therapy, including in utero therapy.³² PACs have low diagnostic yield for CHD 0.3% but may precede more malignant arrhythmias.³²

NONCARDIAC CONGENITAL ANOMALIES

For noncardiac major congenital anomalies, regardless of genetic etiology, we strongly recommend a fetal echocardiogram. If there is a known or suspected chromosomal abnormality, aneuploidy, deletion/duplication, single-gene mutation, or rearrangement of the fetus, a fetal echocardiogram is indicated.

The incidence of CHD in the presence of 1 or more extracardiac malformations is estimated to be 20% to 45% and the risk varies by abnormalities present. CHD is seen in up to 70% of fetuses with genitourinary abnormalities, 30% of omphaloceles, 30% with a congenital diaphragmatic hernia, 20% with duodenal atresia, and 5% to 15% of fetuses with a central nervous system abnormality.⁵

Not all societies agree on screening for a single umbilical artery, we consider a fetal echocardiogram, since there is an incidence of CHD, up to 3.9%.³³ Similarly, fetal venous anomalies may be associated with cardiac abnormalities,

especially with agenesis of ductus venosus (DV), and this risk is slightly greater than our screening threshold.

NONIMMUNE HYDROPS FETALIS

Similarly, to the indication for fetal echocardiogram for major structural anomalies, fetal hydrops confers an indication for referral for a fetal echocardiogram. Cardiac abnormalities are the most common cause of nonimmune hydrops (15%-25% of hydrops caused from CHD or cardiac arrhythmia). Hydrops is presumed to occur because of increased venous pressure from volume overload due to valve regurgitation, pressure overload from outflow obstruction, and decreased diastolic filling time during tachycardia.³⁴

INCREASED NUCHAL TRANSLUCENCY

The correlation with an increased nuchal translucency (NT) with aneuploidy and CHD is well established.³⁵ In the setting of a normal karyotype (no aneuploidy) but an increased NT, the risk of CHD is 1% to 3% if the NT is greater than the 95th percentile (3.0 mm) and 6% if the NT is greater than the 99th percentile (3.5 mm). A fetal echocardiogram should be performed if the NT is at least 3.5 mm and considered if at least 3.0 mm and less than 3.5 mm. The risk of CHD rises exponentially with increasing NT: 24% if greater than 6.0 mm and 60% if greater than 8.5 mm. A body of literature recommends interrogation of the DV to risk stratify a thickened NT. An abnormal DV with an NT greater than 3.0 mm but less than 3.5 mm increases the diagnostic yield for major CHD to 15%.

MONOCHORIONIC PLACENTATION

The incidence of CHD with monochorionic (mono and diamniotic) twin pregnancies is 2% to 9%.^{36,37} This includes monochorionic twins affected and unaffected by twin-twin transfusion syndrome (TTTS), which occurs in 10% of monochorionic twins. TTTS is associated with both acquired right ventricular outflow tract abnormalities and myocardial changes in the recipient twin. Independent of TTTS, monochorionic twins are at increased risk of CHD, specifically ventricular septal defects, pulmonary stenosis, and ASDs.^{36,38}

The risk of fetal CHD when the mother has cardiac disease ranges from 3% to 7%; however, this varies by the underlying lesion of the mother.

FAMILY HISTORY THAT WOULD TRIGGER A FETAL ECHOCARDIOGRAM

A first-degree relative with congenital heart disease, specifically, maternal cardiac disease, is associated with an increased incidence of fetal CHD. Here we focus on nonsyndromic causes of CHD. The risk of fetal CHD when the mother has cardiac disease ranges from 3% to 7%; however, this varies by the underlying lesion of the mother and is highest for a maternal history of aortic stenosis at 13% to 18%, heterotaxy, and AV septal defects have a 10% to 14% risk, and Tetralogy of Fallot is less than 3%.⁵ The risk of cardiac malformation if the father is affected is 2% to 3% and similarly the recurrence risk varies with

lesion type and is highest with aortic stenosis. With an affected sibling (or a previous pregnancy affected with CHD), the risk of recurrence of CHD is lower than that of an affected parent and is 2% to 6%. The risk of CHD increases if more than 1 sibling is affected. The overall risk of fetal CHD is lower with second- and third-degree relatives, with an OR of 1.39 (95% CI, 1.25-1.54) for a second-degree and OR, 1.18 (95% CI, 1.05-1.32) for a third-degree relative.

Counseling on specific genetic disorders, single gene disorders, and syndromes in a parent with any familial history should be personalized and counseling revolves around the underlying genetics and heritability of risk of the disorder/syndrome. Counseling depends on the gene's inheritance patterns and is nuanced by incomplete penetrance, and variable expressivity of the genetics that does require personalized counseling based on etiology. Similarly, if the parent is affected

by an autosomal dominant or recessive genetic disorder with increased risk for cardiac malformations, this also changes the counseling about inheritance. Personalized counseling for risk recurrence should occur with pregnancies with deletion or duplication syndromes known to be associated a significant incidence of abnormal cardiac phenotypes (eg, DiGeorge, Turner syndromes). ■

FOR REFERENCES VISIT
contemporaryobgyn.net/fetal-echocardiogram