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Progress in Pediatric Cardiology 58 (2020) 101259

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

The evolution of fetal echocardiography before and during COVID-19

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ARTICLE INFO

Keywords:
Fetal echocardiography
COVID-19
Indications
Risk factors
Fetal tele-echocardiography

ABSTRACT

The World Health Organization declared the novel coronavirus, or COVID-19, a pandemic in March 2020. Given the severity of COVID-19, appropriate use criteria have been implemented for fetal echocardiography. Screening low risk pregnancies for critical congenital heart disease has typically been a shared responsibility by pediatric cardiologists, obstetricians, and maternal fetal medicine (MFM). Currently, many of the fetal echocardiograms for low risk pregnancies for critical congenital heart disease have been deferred or cancelled with the emphasis on suspected abnormalities by MFMs and obstetricians. In this review, we discuss the literature that has been the basis of screening of low risk pregnancies by pediatric cardiologists. A new approach to more widespread usage of fetal tele-echocardiography may play a large part during COVID-19 and may continue after the pandemic.

1. Introduction

In 2019, a novel coronavirus, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified [1]. The World Health Organization (WHO) later named this novel coronavirus disease COVID-19 and in March 2020, characterized it as a pandemic [2]. In China, pediatric patients with COVID-19 demonstrated effective person-to-person transmission, as did the adult studies. Though children of all ages were found to be sensitive to COVID-19, the pediatric cases were found to be less severe than the adult patients. However, infants were noted to be particularly vulnerable to COVID-19 [3] and more recently, there have been reports of children with an atypical Kawasaki disease presentation with multi-organ system inflammation who have been COVID-19 positive or antibody positive [4]. Given the severity of the COVID-19 pandemic, appropriate use criteria have been implemented for echocardiography, including fetal echocardiography, in order to decrease the risk of exposure and transmission to the mother, fetus, and healthcare provider.

Screening low risk pregnancies for critical congenital heart disease has typically been a shared responsibility by pediatric cardiologists, obstetricians, and maternal fetal medicine (MFM). Currently, many of the fetal echocardiograms for low risk pregnancies for critical congenital heart disease have been deferred or cancelled with the emphasis on suspected abnormalities by MFMs and obstetricians. New recommendations place more emphasis on screening by MFM and obstetricians at a time when the guidelines from the American Institute of Ultrasound in Medicine (AIUM) for performing fetal echocardiography have expanded [5]. In this review, we discuss the literature that has been the basis of screening of low risk pregnancies by pediatric cardiologists. A new approach to more widespread usage of fetal tele-echocardiography may play a large part during COVID-19 and may continue after the pandemic.

The following indications and guidelines for fetal echocardiography reference previous publications by the American Heart Association (AHA), American Society of Echocardiography (ASE) [6], and AIUM.

2. Indications for fetal echocardiography

Multiple factors are associated with increased risk of congenital heart disease (CHD) in the fetus. Referrals for suspected CHD on fetal ultrasound result in a diagnosis of congenital heart disease up to 40% to 50% of the time [7,8]. Patients are referred to screen for CHD due to maternal, familial, or fetal risk factors. (Table 1) Fetal echocardiography should be performed where the risk is > 3% and is reasonable to perform for risk levels ≥2% to 3%. The benefit of fetal echocardiography is less clear when risk is 1% to 2%, and is not indicated when the risk approaches ≤1% [7].

2.1. Maternal risk factors

Maternal risk factors include specific metabolic disorders, such as diabetes mellitus and phenylketonuria. Maternal diabetes increases the risk of congenital heart disease overall [9], but there is an even higher risk with poor control and elevated hemoglobin A1c levels early in

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https://doi.org/10.1016/j.ppedcard.2020.101259
Received 15 May 2020; Received in revised form 15 June 2020; Accepted 16 June 2020
Available online 22 June 2020
1058-9813/

Table 1
Risk factors for congenital heart disease as indicated by AHA, ASE, and AIUM guidelines for fetal echocardiography.

	Associated risk for CHD
Maternal risk factors	
Pregestational diabetes mellitus [7,11]	
Hemoglobin A1c < 6%	< 1%
Hemoglobin A1c > 6.3%	2.5–6.1%
Phenylketonuria [12,13]	
Phenylalanine level > 10 mg/dL	12%
Anticonvulsants [14,15]	< 2%
Selective serotonin reuptake inhibitors [16,17,57]	
Paroxetine	1–2%
Nonsteroidal anti-inflammatory agents	
Ductal constriction [18,19]	Up to 50%
Retinoic acid [21]	8%
Lithium [22]	< 2%
Assisted reproductive technology [25–27]	1.2–3.1%
Viral infections [24,58]	1–2%
SSA/SSB antibodies [32–34]	
Congenital heart block	1–5%
Familial risk factors	
Maternal congenital heart disease [37,38]	
Tetralogy of Fallot	≤3%
Atrioventricular septal defects	10–14%
Previous child or fetus with congenital heart disease [39,40]	2%
Fetal risk factors	
Suspected CHD on obstetric or MFM ultrasound [8]	40–50%
Extracardiac anomalies [43,46]	Variable, 20–45% depending on the organ system affected
Chromosomal abnormalities [8]	Variable, up to 94% depending on the chromosomal disorder
Increased nuchal translucency	
Between 2.5- and 3.4 mm [47]	2.5%
≥3.5 mm [47]	7%
> 6 mm [48]	24%
> 8.5 mm [7,47]	> 60%
Fetal arrhythmias	
Tachycardia [51,56]	1% with associated CHD
Bradycardia (secondary to congenital heart block) [55]	50–55%

pregnancy [10]. Hemoglobin A1c levels above the normal range (> 6.3%) have been associated with an increased risk of cardiac malformations of 2.5% to 6.1% [11]. Untreated maternal phenylketonuria can have up to a 12% incidence if appropriate control is not attained by 10 weeks of gestation [12]. However, if maternal serum levels of phenylalanine are controlled, especially pre-conception and during the first trimester, the risk of congenital heart disease is significantly decreased and fetal echocardiography may not be indicated [13].

Exposure to teratogens, such as anticonvulsants, selective serotonin reuptake inhibitors (SSRIs), nonsteroidal anti-inflammatory agents (NSAIDs), retinoic acid, lithium, and alcohol, have been reported to increase the risk for congenital heart disease. Previous studies have shown the risk of CHD with exposure to anticonvulsants is < 2% [14,15]. Specifically, valproic acid has been associated with congenital heart disease. Exposure to valproic acid during the first trimester has been shown to increase the risk of atrial septal defects by 2 to 7 times, however, the associated risk is low at 0.5% [15]. Previous studies have shown that the use of most SSRIs in pregnancy is not associated with an increased risk for congenital heart disease [16]. Paroxetine, however, may be an exception when exposure is during the first trimester [17], though the overall risk of CHD with paroxetine exposure still remains low. Thus if there is maternal exposure to paroxetine, fetal echocardiography can be considered.

Nonsteroidal anti-inflammatory medications may result in intrauterine ductal constriction [18,19]. Fetal echocardiography is recommended for NSAID use during the second and third trimesters. Exposure to NSAIDs earlier in pregnancy has been associated with a small increase in congenital heart disease [20], however the usefulness of fetal echocardiography in these patients has not been established. Retinoic acid is contraindicated in pregnancy; congenital heart abnormalities including conotruncal defects and aortic arch anomalies were reported in 8% of exposed fetuses in previous studies [21]. Recent reports on exposure to lithium during pregnancy have suggested that the risk of congenital heart disease is < 2%, which is less than previously thought. Though an association cannot be ruled out, one study found no difference in the number of anomalies between patients treated with lithium and control patients [22]. In cases with exposure to lithium, fetal echocardiography may be considered, however its efficacy has not been established. Prenatal alcohol exposure is not associated with overall CHD, as previous studies have found no increased risk of malformations in women who consume 1 to 2 drinks per day. However, moderate drinking may have a marginal association with conotruncal anomalies, though the significance of this association varies [23,24].

There is an increased risk of congenital heart disease in infants conceived via assisted reproductive technology (ART) as compared with pregnancies conceived spontaneously [25,26]. Ventricular septal defects were more frequent with in vitro fertilization, whereas tetralogy of Fallot and transposition of the great arteries were more common in spontaneously conceived pregnancies [26]. An association with atrial septal defects and assisted reproductive technology has also been described [28]. Overall, the risk of CHD with ART varies between 1.2% and 3.1% [25–27].

The risk of cardiac malformations with maternal viral infections is 1–2%. Specific viral infections, such as rubella, increase the risk for congenital heart disease especially when infection occurs early in pregnancy. The most common associated cardiac lesions with maternal rubella are patent ductus arteriosus, ventricular septal defects, and branch pulmonary artery stenosis [24,29]. Maternal infection with parvovirus may cause dilated cardiomyopathy and inflammatory cell infiltration of the myocardium with subendocardial fibroelastosis [30].

Maternal autoantibodies, specifically anti-Ro and anti-La, are associated with lupus erythematosus and Sjögren's syndrome and increase risk for the fetal atrioventricular block [31]. Previous studies have reported an incidence of fetal congenital heart block of 1% to 5% [32–34]. Subsequent pregnancies may have a risk as high as 20% after having a child with complete heart block in a previous pregnancy.

2.2. Familial risk factors

Family history of a first degree relative with congenital heart disease is typically associated with an overall 2–3 times increased risk as compared to the general population. When CHD is present in the mother the risk varies depending on the specific maternal diagnosis. The risk for fetal congenital heart disease is higher with maternal atrioventricular septal defects, as compared to other lesions such as tetralogy of Fallot in the absence of genetic abnormalities, where the risk is much lower [35,36]. The risk with atrioventricular septal defects has been reported up to 10% to 14%, whereas the risk with isolated tetralogy of Fallot has been reported as ≤3% [37,38]. Many of the early studies predicting incidence were in an era where genetic abnormalities were not excluded as the risk factor rather than the presence of CHD. Previous history of a child or fetus with CHD increases the risk for CHD in a subsequent pregnancy to 2% [39,40]. Specific malformations are associated with an increased risk of recurrence, such as left heart obstructive syndromes and heterotaxy [41].

2.3. Fetal risk factors

Additional increased risk factors for which fetal echocardiography should be considered include fetal risk factors. If the fetus is found to

have an extracardiac anomaly, the heart should be closely examined [42], as the risk for associated CHD can vary between 20 and 45%, depending on the organ system affected [43,44]. Abnormalities which have been associated with congenital heart disease include omphaloceles, congenital diaphragmatic hernias, duodenal atresia, single umbilical artery, tracheoesophageal fistula, or fetal hydrops. Additionally, if a chromosomal abnormality, such as aneuploidy, has been identified, the fetus also has an increased risk of congenital anomalies. Thus, fetal echocardiograms are recommended for these patients [8].

Nuchal translucency is a subcutaneous collection of fluid seen in the posterior neck at 10 to 14 weeks of gestation. Increased nuchal translucency has been shown to correlate with an increased risk of aneuploidy and other congenital malformations [44]. An association between increased nuchal translucency and congenital heart disease in chromosomally normal fetuses has been reported as well [45]. The risk for congenital heart disease increases as the nuchal translucency measurement increases. In fetuses with nuchal translucency between 2.5 and 3.4 mm, ≥3.5 mm, > 6 mm, and > 8.5 mm, the incidence of major CHD was reported to be 2.5%, 7%, 24%, and > 60%, respectively [7,47,48]. Based on current data, the American Heart Association recommends fetal echocardiography for fetuses with a nuchal translucency ≥3.5 mm, and states that it is reasonable to perform for fetuses with a nuchal translucency ≥3.0 mm to 3.5 mm. Fetal echocardiography is not indicated in fetuses an a nuchal translucency < 3.0 mm [7].

Abnormal cardiac rhythms in the fetus also result in referral for fetal echocardiography. Specifically, fetal bradyarrythmias, especially when secondary to congenital heart block, have been associated with congenital heart disease in up to 59% of cases [49]. Isolated atrial extrasystoles have a low association with congenital heart disease and are hemodynamically benign, however they can precipitate supraventricular tachycardia in susceptible fetuses [50]. Occasional ventricular extrasystoles are also thought to be of limited significance, though if frequent, require further assessment [51].

The presence of a two vessel cord, or a single umbilical artery, and venous abnormalities, have been associated with increased risk of congenital heart disease, though the incidence has not been clearly defined. Absence of the ductus venosus can lead to chronic volume overload and the risk of high-output heart failure in the fetus due to unimpeded placental return as the umbilical veins drain through alternative low-resistance pathways [52]. Therefore, fetal echocardiography can be considered in both anomalies, though specific usefulness has not been established.

3. Timing for fetal echocardiograms

Fetal echocardiograms for screening of pregnancies at risk for congenital heart disease occur between 18 and 22 weeks of gestation. However, fetal echocardiography during this period may miss congenital heart disease that progresses throughout the pregnancy, as well as arrhythmias, which typically arise later in the second or the third trimester [45]. If routine ultrasounds by obstetricians are concerning for cardiac anomalies, patients should be referred urgently. If congenital heart disease is then identified, serial fetal echocardiography is recommended. Fetal echocardiography can also be performed prior to 18 weeks gestation for those at the highest risk for congenital heart disease, or for families who have a significant history of a previous child with congenital heart disease [15].

4. Fetal echocardiography guidelines during COVID-19

To comply with the social distancing recommendations made by the CDC, our institution limited in-person fetal heart consultations and on-site fetal echocardiography exams unless there was an urgency or risk to the fetus which outweighed the benefits. Patients were grouped into three different categories based on their level of risk. These guidelines were created based on the recommendations for fetal echocardiography during COVID-19 by the American Society of Echocardiography (ASE) [[54]]. Patients were triaged by the director of fetal cardiology and/or the division chief of cardiology after discussion with the MFM and/or obstetric team. Patients who were low risk were grouped into Category 1 and were rescheduled for a later time. These patients included pregestational diabetes, in-vitro fertilization, family or maternal history of congenital heart disease, medication exposure, single umbilical artery, premature atrial beats, routine follow-up for twin-twin transfusion syndrome after laser with no major cardiovascular concerns, or follow-up from an earlier fetal cardiovascular imaging study.

Category 2 comprised of those who needed to be seen non-urgently. This included pregnancies with suspected non-critical congenital heart disease, follow up for congenital heart disease less than 34 weeks, maternal anti-Ro antibody follow up after 20 weeks if they had a home monitor, second opinions for fetal heart disease already identified, or any other second opinions.

Patients who were considered urgent or essential were placed into Category 3 and were seen at the next available appointment. These patients were those with critical congenital heart disease diagnosed or suspected by MFM, any genetic or extracardiac anomalies that required cardiac assessment, new twin-twin transfusion syndrome, or follow up of twin-twin transfusion syndrome after laser if there were major cardiovascular concerns, fetal supraventricular tachycardia or ventricular tachycardia, an early fetal echocardiogram with a high-risk indication, or final visits for known congenital heart disease if greater than 34 weeks.

COVID-19 has limited the amount of screening for CHD that is being performed by pediatric cardiologists via fetal echocardiography for lower risk populations or those with less than or equal to a 3% risk. This coincides with the AIUM revising their practice parameters for the performance of fetal echocardiography in 2020. However, though these practice parameters have been advanced, for example to include axial sweeps, fetal echocardiography practices by pediatric cardiologists still differ as the latter would also include sagittal sweeps. Thus, the role of the pediatric cardiologist may continue to evolve educationally in order to support the goal of a more comprehensive evaluation occurring in the obstetrician and MFM office during and after COVID-19.

Education and care may be further enhanced with fetal tele-echocardiography, or the ability to guide obstetrical sonographers through a complete evaluation remotely, in conjunction with a telehealth consult with the family. The telehealth consult may be scheduled with a pediatric cardiologist and a congenital heart surgeon. Telehealth consultations, while not allowing the physicians to be directly present with a family during a stressful time, may become a new norm during a time of risk to patients and healthcare providers. Fetal tele-echocardiography can be advantageous as it allows a more timely approach to diagnosis with an obstetrician or MFM having the ability to remotely obtain 24/7 access to a pediatric cardiologist. Additionally, telehealth software and the use of video capture adapters may provide a relatively simple approach to live imaging, as fetal echocardiograms can then be streamed to a picture archiving and communication system (PACS) for reading. The former allows the pediatric cardiologist to remotely be involved in obtaining a complete fetal echocardiogram. Screening fetal echocardiography and scanning for diagnosed CHD after COVID-19 may be forever changed. A prospective study to evaluate the efficacy of a telehealth program for fetal echocardiography with a robust educational program for sonographers and physicians is warranted during COVID-19 and beyond the pandemic.

Declaration of competing interest

None.

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