Review Article

An Update on Cardiovascular Malformations in Congenital Rubella Syndrome

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Received 18 May 2009; Revised 21 June 2009, 30 June 2009; Accepted 1 July 2009

BACKGROUND: Congenital rubella syndrome (CRS) has long been characterized by the triad of deafness, cataract, and cardiovascular malformations (CVMs). While initial reports identified patent ductus arteriosus (PDA) as the primary CVM in CRS, the exact nature of the CVMs found in CRS has not been well established. **METHODS**: We searched the English literature from 1941 through 2008 to identify studies that used cardiac catheterization or echocardiography to evaluate the CVMs in CRS. **RESULTS**: Of the 121 patients in the 10 studies with catheterization data, 78% had branch pulmonary artery stenosis, and 62% had a PDA. In 49% of cases, both branch pulmonary artery stenosis and PDA were present, whereas isolated branch pulmonary artery stenosis and isolated PDA were found in 29 and 13% of cases, respectively. Of the 12 patients in the 10 studies with echocardiographic data, PDA was more common than branch pulmonary artery stenosis, but this finding is greatly limited by the small numbers of patients and limitations of echocardiography. Although published studies of CVMs in CRS have in general reported PDA as the CVM phenotype most commonly associated with CRS, among CRS cases evaluated by catheterization, branch pulmonary artery stenosis was actually more common than PDA. Moreover, although the combination of branch pulmonary artery stenosis and PDA was more common than either branch pulmonary artery stenosis or PDA alone, isolated branch pulmonary artery stenosis was twice as common as isolated PDA. **CONCLUSION**: Among children with suspected CRS, clinical evaluations for the presence of CVMs should include examinations for both branch pulmonary artery stenosis and PDA. *Birth Defects Research (Part A) 88:1–8, 2010.* © 2009 Wiley-Liss, Inc.

Key words: rubella; heart; congenital heart defects; cardiovascular malformations; infection; pediatrics; patent ductus arteriosus; branch pulmonary artery stenosis

INTRODUCTION

Congenital rubella syndrome (CRS) has long been associated with the triad of deafness, cataract, and cardiovascular malformations (CVMs) (Gregg, 1945). However, as the diagnosis of congenital CVMs has been based often on clinical examination alone, the exact nature of the spectrum of cardiac phenotypes associated with CRS has not been well established.

Patent ductus arteriosus (PDA) was the predominant CVM noted by Gregg in the initial report of CRS in 1941 (Gregg, 1941). This association was also reported by other clinicians during the following two decades (Gibson and Lewis, 1952; Stuckey, 1956; Bell, 1959). In 1961, Campbell confirmed the association of CRS with PDA in his comprehensive review of the literature, finding that 89 (65%) of 136 cases with CRS and a congenital CVM had a PDA (Campbell, 1961). However, these observations were based primarily on clinical examinations, before the availability of advanced diagnostic techniques such as catheterization or echocardiography. Furthermore, because CRS can also be associated with low birth weight, the extent to which the association of PDA with

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Published online 20 August 2009 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.20621

CRS reflects a coincidental association with preterm delivery versus a direct relationship with CRS is unclear.

As cardiac catheterization became more widely available in the 1950s and awareness of CRS grew, clinicians began to report other cardiac lesions in association with CRS, most notably pulmonary artery stenosis (Jenkins et al., 2007). In 1958, Heiner and Nadas observed that two of six surgically confirmed cases of PDA with pulmonary artery stenosis also had CRS (Heiner and Nadas, 1958). Various catheterization-based studies in the 1960s found that pulmonary artery stenosis was a common CVM in patients with CRS, even in the absence of PDA (Rowe, 1963; Emmanouilides et al., 1964; Venables, 1965; Sperling and Verska, 1966; Hastreiter et al., 1967; Celermajer et al., 1969; Kher et al., 1980). These observations prompted Way (1967) to postulate that pulmonary artery stenosis may be underappreciated as a CVM associated with congenital rubella. However, there has been no systematic review of the literature regarding CVMs associated with rubella since Campbell's 1961 article.

While the widespread use of technological advances such as cardiac catheterization in the 1950s (Bourassa, 2005) and echocardiography in the 1980s (Krishnamoorthy et al., 2007) have improved the ability to diagnose CVMs, the prevalence of CRS has sharply decreased since the introduction of the rubella vaccine in 1968 (Mueller, 1968), thus making modern assessments of the CVMs associated with CRS difficult. Nevertheless, rubella infection during pregnancy remains an important risk factor for congenital CVMs worldwide, especially in many developing countries (Cutts et al., 1997). For instance, the World Health Organization estimates that every year there are at least 100,000 new cases of CRS worldwide (Robinson et al., 2006), of which 70% could potentially have a CVM (Rittler et al., 2004). Therefore, we sought to better identify the CVM phenotypes associated with rubella by performing a critical review of the literature, concentrating on those studies that used cardiac catheterization or echocardiography in evaluation of patients with CRS. By convention, we included CVMs of the great vessels in our analysis.

MATERIALS AND METHODS

We used PubMed to search Medline, considering articles published between 1950 and 2008 that matched the terms ''rubella *and* heart'' or ''congenital rubella syndrome'' and were limited to subjects under the age of 18. In addition, we examined the bibliographies of these articles to identify additional articles of interest, including articles published as early as Gregg's initial report of CRS in 1941. From this set of articles, those which met the following criteria were included in our review: (1) utilized either cardiac catheterization or echocardiography to establish the diagnosis of a CVM and (2) reported either maternal history of or laboratory confirmation of rubella infection. Autopsy results (n = 6) were not included because of an effort to minimize biasing results toward the most lethal lesions and because of the limitation of autopsies to diagnose stenosis in the absence of blood flow.

RESULTS

Our search identified 792 articles, very few of which utilized catheterization or echocardiography. There were 19 articles that met the inclusion criteria and contained sufficient data available for review. Of these, nine were based on catheterization data alone (Rowe, 1963; Emmanouilides et al., 1964; Venables, 1965; Sperling and Verska, 1966; Hastreiter et al., 1967; Celermajer et al., 1969; Lie et al., 1970; Kher et al., 1980; Gorenflo et al., 2002), nine on echocardiographic data alone (Janner, 1991; Robinson et al., 1994; Bullens et al., 2000; St John and Benjamin, 2000; Agarwal et al., 2001; Banerji et al., 2005; Koklu et al., 2006; Wui et al., 2006; Plotinsky et al., 2007), and one on both catheterization and echocardiographic data (Moore and Mullins, 1986) (Fig. 1).

The 10 articles with catheterization data reported findings on 121 patients (Table 1). Of these, 75 patients (62%) had a PDA, and 94 (78%) had some degree of branch pulmonary artery stenosis. Both branch pulmonary artery stenosis and PDA were present in 59 cases (49%), whereas PDA without branch pulmonary artery stenosis was found in 16 cases (13%) and branch pulmonary artery stenosis without PDA in 35 cases (29%). Other cardiac lesions, such as atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous return, pulmonary atresia, aortic isthmus hypoplasia, subaortic membrane, and heterotaxy (unspecified), were occasionally reported.

Of the 94 cases of branch pulmonary artery stenosis, information regarding sidedness was available for 25 (Table 2). Catheterization revealed bilateral branch pulmonary artery stenosis in 18 cases (72%). In seven of the cases (28%), however, there was unilateral branch pulmonary artery stenosis, and it was always right-sided.

As part of the catheterization of patients with CRS, several authors described a distinctive angiographic picture of branch pulmonary artery stenosis in CRS. Hastreiter described a ''characteristic picture'' of the right pulmonary artery in patients with CRS: the right pulmonary artery was ''elongated, rather rigid and tubular, and its branches appeared to originate more peripherally than normal. The right upper lobe branch was frequently stenotic at its origin and tended to course more horizontally, as if an extension of the right main branch'' (Hastreiter et al., 1967). Similarly, Celermajer found that in patients with CRS and pulmonary arterial stenosis in the absence of a PDA, there were ''markedly hypoplastic pulmonary artery branches with a moderate-sized pulmonary trunk '' (Celermajer et al., 1969). In each of the cases studied by Venables, angiography revealed

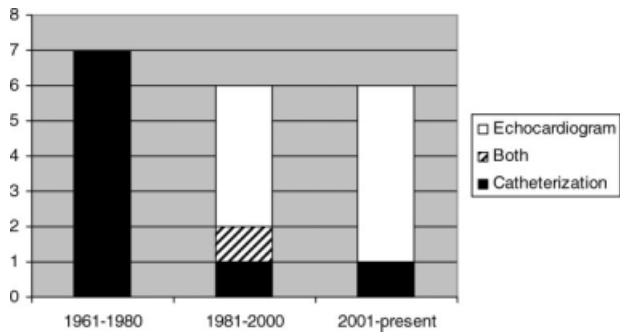

Figure 1. Number of studies during each time period examining heart defects in congenital rubella syndrome utilizing cardiac catheterization, echocardiogram, or both.

Table 1
Cardiac Catheterization Findings in Selected Articles on Congenital Rubella Syndrome and Congenital Heart Defects

Lesion	N (%)	Rowe et al., 1963	Emmanoulides et al., 1964	Venables, 1965	Sperling et al., 1966	Hastreiter et al., 1967	Celermajer et al., 1969	Lie et al., 1970	Kher et al., 1980	Moore et al., 1986	Gorenflo et al., 2002
Branch pulmonary artery stenosis											
Isolated	18 (15%)	0	0	0	1	6	11	0	0	0	0
+ PDA	40 (33%)	1	2	0	3	24	9	0	1	0	0
+ PDA + pulmonary valve stenosis	9 (7%)	1	3	1	0	4	0	0	0	0	0
+ PDA + other intracardiac lesion	8 (7%)	0	1	1	0	3	2	0	0	1	0
+ PDA + systemic arterial lesion	1 (1%)	0	0	0	0	0	1	0	0	0	0
+ PDA + pulmonary valve stenosis + systemic arterial lesion	1 (1%)	1	1	0	0	0	0	0	0	0	0
+ Pulmonary valve stenosis	7 (6%)	6	0	1	0	0	0	0	0	0	0
+ Pulmonary valve stenosis + other intracardiac lesion	2 (2%)	2	2	0	0	0	0	0	0	0	0
+ Other cardiac lesion[a]	6 (5%)	0	0	0	0	0	6	0	0	0	0
+ Systemic arterial lesion	2 (2%)	0	0	0	0	0	2	0	0	0	0
PDA without branch pulmonary artery stenosis	10 (8%)	0	0	0	1	0	4	2	2	0	1
Isolated											
+ Pulmonary valve stenosis	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ Pulmonary valve stenosis + other intracardiac lesion	1 (1%)	0	0	0	0	0	0	0	1	0	0
+ Other cardiac lesion[a]	5 (4%)	0	0	0	0	0	5	0	0	0	0
No PDA or branch pulmonary artery stenosis											
Other cardiac lesions[a]	7 (6%)	0	0	0	2	0	5	0	0	0	0
Isolated systemic arterial lesions	1 (1%)	0	0	0	0	0	1	0	0	0	0
Isolated myocardial lesions	3 (2%)	0	0	0	0	0	3	0	0	0	0
Total	121	11	6	3	7	37	49	2	4	1	1

[a]Other cardiac lesions include atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous return, pulmonary atresia, aortic isthmus hypoplasia, subaortic membrane, and heterotaxy (unspecified).
PDA = patent ductus arteriosus.

Table 2
Findings on Sidedness of Branch Pulmonary Artery Stenosis in Articles on Congenital Rubella Syndrome and Congenital Heart Defects

Year of publication	Authors	PAS-RPA	PAS-LPA	PAS-bilateral	Total branch PAS
1963	Rowe et al.	2	0	9	11
1964	Emmanoulides et al.	1	0	5	6
1965	Venables	0	0	3	3
1966	Sperling and Verska	3	0	1	4
1980	Kher et al.	1	0	0	1
	Total N (%)	7 (28%)	0 (0%)	18 (72%)	25 (100)

PDA = patent ductus arteriosus; PAS = pulmonary artery stenosis; LPA = left pulmonary artery; RPA = right pulmonary artery.

''bilateral narrowing of the main pulmonary artery branches at least at their origin from the main pulmonary artery'' (Venables, 1965).

The 10 articles with echocardiographic data reported findings on only 12 patients (Table 3). Of these, eight patients (67%) had a PDA and three (25%) had some degree of branch pulmonary artery stenosis. Both branch pulmonary artery stenosis and PDA were present in one case (8%), whereas PDA without branch pulmonary artery stenosis was found in seven cases (58%) and branch pulmonary artery stenosis without PDA in two cases (17%). Other cardiac lesions, such as atrial septal defect, ventricular septal defect, Ebstein's anomaly, and subaortic membrane, were occasionally reported.

DISCUSSION

As the number of patients with CRS in whom echocardiographic findings are available is quite small, we must therefore draw conclusions regarding CVMs in CRS primarily from catheterization data. While most published studies have reported PDA as the CVM most commonly associated with CRS, our comprehensive review shows that, when the CVMs are evaluated by catheterization, branch pulmonary artery stenosis is more common than PDA. In the catheterization-based studies on CRS, branch pulmonary artery stenosis in association with PDA was more common than either branch pulmonary artery stenosis or PDA alone, and isolated branch pulmonary artery stenosis was twice as frequent as isolated PDA. Furthermore, although branch pulmonary artery stenosis was usually bilateral, those cases that were unilateral were all right-sided, a finding that is supported by angiographic evidence as well (Venables, 1965; Elliott and Amplatz, 1966; Hastreiter et al., 1967; Celermajer et al., 1969).

The perception that PDA is much more common than branch pulmonary stenosis in our review of the limited echocardiographic findings may be due to (1) the reliance of earlier studies to suggest PDA being most common and (2) the limitations of echocardiography. Unless the echosonographer is intently using Doppler interrogation to evaluate for the presence of branch pulmonary stenosis, this finding may be missed on a routine echocardiogram. Furthermore, it is not uncommon for an echocardiographic evaluation to give a false-negative diagnosis in a patient with branch pulmonary artery stenosis (Sueblinvong, 1990).

We believe that the disparity between the findings in our catheterization-based review and previous reports of PDA being the most common CVM associated with CRS exists for three reasons: (1) the fact that initial studies found PDA associated with CRS, thereby setting the precedent for future reports, (2) the lack of objective studies such as catheterization or echocardiography to support the diagnosis, and (3) the use of PDA as a selection criterion for identifying patients with CRS. The initial reports of Gregg in 1941 and others in the 1950s identified PDA as the most common CVM in CRS. These observations were based primarily on clinical observations in the absence of any definitive diagnostic tool such as cardiac catheterization or echocardiography, which were not available at the time. Many subsequent researchers used PDA as a selection criterion to identify possible patients with CRS in the absence of confirmatory laboratory testing. It was not until the widespread availability of cardiac catheterization that definitive diagnoses of CVMs could be made in patients suspected of having cardiac disease.

Prematurity and low birth weight warrant some consideration as potential confounders in determining the relationship of CRS with PDA or branch pulmonary artery stenosis. It is possible that some of the initial studies of the heart defects in CRS may have considered the association of CRS with PDA as a causal one, when, in fact, the association may have been an indirect one since CRS can result in prematurity (Lanzieri et al., 2004) and low birth weight (Korones et al., 1965; Rittler et al., 2004), and prematurity in turn often results in PDA. It is unclear to what extent PDA occurs in term babies with CRS and birth weights that are appropriate for gestational age. One recent analysis of a rubella epidemic in Texas controlled for low birth weight by excluding infants with birth weight <2500 gm, but this retrospective study included only two confirmed cases of PDA (Zimmerman and Reef, 2001). Similarly, both CRS and branch pulmonary artery stenosis are associated with prematurity and low birth weight (Rodriguez and Riggs, 1990). Although branch pulmonary artery stenosis usually regresses through infancy (Prieto, 2008), the presence of this CVM among children older than seven months in our review may indicate a true pathologic abnormality (Rowe, 1963; Emmanouilides et al., 1964; Kher et al., 1980; Gorenflo et al., 2002). Unfortunately, there were insufficient data in the reviewed articles to examine the independent and joint effects of CRS and prematurity or low birth weight on the prevalence of PDA or other CVMs.

The precise mechanism by which rubella infection during pregnancy may lead to branch pulmonary artery

Table 3
Echocardiographic Findings in Selected Articles on Congenital Rubella Syndrome and Congenital Heart Defects

Lesion	N (%)	Moore et al., 1986	Janner, 1991	Robinson et al., 1994	Bullens et al., 2000	St John et al., 2000	Agarwal et al., 2001	Banerji et al., 2005	Koklu et al., 2006	Wui et al., 2006	Plotinsky et al., 2007
Branch pulmonary artery stenosis											
Isolated	2 (17%)	0	0	0	0	1	0	0	1	0	0
+ PDA	0 (0)%)	0	0	0	0	0	0	0	0	0	0
+ PDA + pulmonary valve stenosis	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ PDA + other intracardiac lesion	1 (8%)	1	0	0	0	0	0	0	0	0	0
+ PDA + systemic arterial lesion	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ PDA + pulmonary valve stenosis + systemic arterial lesion	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ Pulmonary valve stenosis	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ Pulmonary valve stenosis + intracardiac lesion	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ Other cardiac lesion[a]	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ Systemic arterial lesion	0 (0%)	0	0	0	0	0	0	0	0	0	0
PDA Without branch pulmonary artery stenosis											
Isolated	4 (33%)	0	0	1	1	1	0	0	0	0	1
+ Pulmonary valve stenosis	1 (8%)	0	0	0	0	0	0	1	0	0	0
+ Pulmonary valve stenosis + other intracardiac lesion	0 (0%)	0	0	0	0	0	0	0	0	0	0
+ Other cardiac lesion[a]	2 (17%)	0	1	0	0	0	1	0	0	0	0
No PDA or branch pulmonary artery stenosis											
Other cardiac lesions[a]	2 (17%)	0	0	0	0	1	0	0	0	1	0
Isolated systemic arterial lesions	0 (0%)	0	0	0	0	0	0	0	0	0	0
Isolated myocardial lesions	0 (0)%)	0	0	0	0	0	0	0	0	0	0
Total	12	1	1	1	1	3	1	1	1	1	1

[a]Other cardiac lesions include atrial septal defect, ventricular septal defect, Ebstein's anomaly, and subaortic membrane.
PDA = patent ductus arteriosus.

stenosis or PDA remains unknown. Although excluded from our analysis, pathologic studies do offer some insights into potential mechanisms. Some pathologic studies evaluating vascular specimens of patients with congenital rubella have shown significant pulmonary artery hypoplasia (Tang et al., 1971), whereas others have found extensive arterial intimal fibromuscular proliferation of both the pulmonary and systemic circulation (Esterly and Oppenheimer, 1967, 1969; Singer et al., 1967; Rosenberg, 1987; Webster, 1998). When present, this intimal proliferation is thought to play a role in pulmonary artery stenosis. Tang postulated that pulmonary arteries may become hypoplastic due to primary growth failure, a phenomenon that has been documented by Naeye and Blanc (Naeye and Blanc, 1965). The stenosis of the hypoplastic arteries may worsen because of intimal proliferation resulting from hemodynamic stresses associated with flow through the PDA (Tang et al., 1971). The concept of a progressively worsening branch pulmonary artery stenosis is supported by Waller's description of a 27-year-old patient with CRS who was found at autopsy to have many discrete stenoses of the pulmonary arteries (Waller et al., 1982). Some pathologic evaluations of PDA in CRS have shown a thin muscular wall with abnormal development of the internal elastic lamina (Swan, 1944; Campbell, 1965; Webster, 1998). It is also possible that, although the pulmonary artery stenosis may worsen in the setting of a PDA, the PDA may be an obligatory shunt lesion, allowing for adequate pulmonary blood flow in the presence of obstruction. Thus, in some cases the PDA may be secondary to the pulmonary artery stenosis, and not a direct consequence of the CRS.

Although branch pulmonary artery stenosis and PDA may be the predominant CVMs associated with CRS, other less-frequently associated CVMs have been noted (Campbell, 1961; Korones et al., 1965; Tondury and Smith, 1966; Singer et al., 1967; Esterly and Oppenheimer, 1969; Tang et al., 1971; Rowe, 1973; Rosenberg et al., 1981; Rosenberg, 1987) including tetralogy of Fallot, coarctation of the aorta, aortic stenosis, transposition of the great vessels, and tricuspid atresia. There are numerous other studies of CRS that list ''congenital heart disease'' as a manifestation of CRS, yet offer no further specification. Since 1980, as the incidence of CRS has decreased, a thorough assessment of the cardiac defects associated with CRS has not been done. Most of the reports during rubella outbreaks commented on congenital CVMs as part of a spectrum of defects in CRS and lack sufficient information to properly evaluate specific cardiac defects (Tokugawa and Ueda, 1986; Cutts et al., 1997; Schluter et al., 1998; St John and Benjamin, 2000; Zimmerman and Reef, 2001; Lanzieri et al., 2004; Al-Awaidy et al., 2006).

The excess risk of congenital CVMs associated with CRS is not known; thus it is difficult to understand the true burden of branch pulmonary artery stenosis or other CVMs. Estimates of the prevalence of CVMs among infants exposed to rubella in utero vary widely from 3 to 75% (Lundstrom, 1962; Sheridan, 1964; Lindquist et al., 1965; Rudolph et al., 1965). In Kato's retrospective review of 362 patients, he found evidence of CVMs in 19.6% of patients with suspected CRS (Kato et al., 1973). However, this is likely an overestimate, as diagnosis of PDA was used as a selection criterion to identify potential patients. Conversely, in Celermajer's review of 117 patients studied prospectively following maternal rubella infection, the prevalence of congenital CVMs associated with rubella was only 9.4% (Celermajer et al., 1969). Variation in prevalence estimates of CRS among births may partially reflect differences in under-ascertainment of affected pregnancies that end in spontaneous or therapeutic abortions, because the occurrence of all malformations is significantly higher when maternal rubella infection occurs in the first trimester (Ingalls and Purshottam, 1953; Pitt and Keir, 1965; Cooper et al., 1969; Siegel et al., 1971; Ueda et al., 1979; Miller et al., 1982; Peckham, 1985). Campbell reported a risk of CVMs of 30–70% when maternal rubella infection occurs during the first four weeks of gestation, 25–55% during the second four weeks, 20–40% during the third four weeks, and 10–25% during the fourth four weeks (Campbell, 1961). Thus, valid estimates of the prevalence of CVMs associated with rubella infection are difficult to obtain, as many mothers infected with rubella may undergo spontaneous or therapeutic abortion. Nevertheless, according to a recent review of nine prospective studies on the frequency of various clinical manifestations among infants with congenital rubella syndrome, about 45% of infants with CRS had some type of CVM (Reef et al., 2000). Based on this estimate and on an estimated prevalence of CVM in the unexposed population of 1%, the proportion of CVMs that might be attributable to congenital rubella infection among infants with CRS is 98% ([RR − 1]/RR = [45–1]/45). Further studies based on large populations and with adequate diagnostic facilities are needed to derive current estimates of the contribution of CRS to the burden of CVMs in the population.

This study has some limitations. First, only patients who had suspected heart disease underwent catheterization. As a result, subclinical CVMs not detectable by routine examination or EKG may not have been identified. Second, although some of the larger catheterization-based studies included mostly prospective patients, the remainder of the catheterization-based studies and all of the echocardiogram-based studies included retrospective case reports. Third, just as earlier studies did not control for birth weight or prematurity, we may be overestimating the frequency of PDA and branch pulmonary artery stenosis associated with CRS by not being able to control for these factors. Finally, most of the catheterization-based studies were conducted 40 years ago. As previously mentioned, there has not been a large, systematic evaluation of CVMs in children with suspected CRS similar to some of the articles reviewed here. This is likely because the prevalence of rubella has dramatically decreased in the last 30 years in areas where cardiac catheterization and echocardiography are readily available and used, thus making it difficult to adequately study the CVMs in CRS.

Despite its declining incidence, CRS is still a problem worldwide, especially in developing countries. Furthermore, there remain episodic outbreaks of infection, with some countries reporting an incidence of CRS as high as 2.2 per 1000 births during an outbreak (Cutts et al., 1997). Thus, in the era of advanced diagnostic tools, our review can guide evidence-based practice in caring for infants with suspected CRS. In areas in which rubella has not been eradicated, clinicians should consider CRS in children with branch pulmonary artery stenosis and PDA, particularly in the presence of eye anomalies, as the combination of CVMs and cataracts appears to offer the best

positive predictive value for CRS (~ 60%) (Reef et al., 2000). In all children in whom CRS is suspected, clinicians should carefully perform a full cardiac evaluation, because in both catheterization and echocardiographic studies a wide-range of lesions were present. Cardiac catheterization, while fully identifying all levels of branch pulmonary artery stenosis, may be unnecessarily invasive. This current review suggests that, when available, echocardiography be performed on all eligible children with suspected CRS to evaluate for CVMs, especially branch pulmonary artery stenosis and PDA. As echocardiographic imaging improves, a large-scale echocardiographic study in children with CRS would be valuable in assessing the burden of CVMs in CRS and in evaluating for a potential pathognomonic echocardiographic feature of CRS, such as the characteristic angiograms noted by Hastreiter et al. (1967). Further study of the CVMs of CRS may contribute to an improved understanding of cardiac embryology and the pathogenic effects of viral illnesses in utero.

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