

REVIEW ARTICLE

Fetal and neonatal abnormalities due to congenital rubella syndrome: a review of literature

Alexandre Yazigi¹, Aurelia Eldin De Pecoulas¹, Christelle Vauloup-Fellous², Liliane Grangeot-Keros², Jean-Marc Ayoubi^{1,3}, and Olivier Picone^{1,3}

¹Department of Obstetrics and Gynecology, Hôpital Foch, Suresnes, France, ²AP-HP, Hôpital Paul Brousse, Groupe Hospitalier Universitaire Paris-Sud, Virologie, WHO Rubella NRL, National Reference Laboratory for Maternofetal Rubella Infections, Univ Paris-Sud, INSERM U1193, Villejuif, France, and ³EA2493; UFR Des Sciences De La Santé Simone Veil, Université Versailles Saint Quentin En Yvelines, Montigny Le Bretonneux, France

Abstract

Objective: Rubella virus infection during the first trimester of pregnancy can cause congenital rubella syndrome (CRS). We aimed to describe the abnormalities in order to define the ultrasound features to look for when performing prenatal scans. The goal of this review is to focus specifically on the signs of CRS accessible to prenatal diagnosis.

Methods: We analyzed every case of CRS described before and/or after birth that we identified in the Pubmed database and classified them as accessible or not to prenatal diagnosis.

Results: The most frequently reported malformations accessible to prenatal diagnosis were: cardiac septal defects, pulmonary artery stenosis, microcephaly, cataract, microphthalmia, and hepatosplenomegaly.

Conclusion: This extensive literature review shows that the ultrasound features of CRS are not well known, even though rubella was the first teratogenic virus described. This review will help clinicians in the management of rubella during pregnancy by clarifying the findings to be sought.

Keywords

Antenatal ultrasound, congenital cataract, congenital heart diseases, congenital rubella syndrome, fetal infection, rubella and pregnancy

History

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Introduction

Rubella is an eruptive, highly contagious, and generally mild viral disease that is unnoticed and without consequences in most cases. Primary infection usually occurs during childhood and provides long-term immunity. Infection during the first trimester of pregnancy can cause a fetal malformation syndrome known as congenital rubella syndrome (CRS) [1–3].

This infection can be prevented effectively by vaccine [2]. The decline in the number of cases of CRS in developed countries may lead to its under-diagnosis [2]. Because countries with widespread antenatal ultrasound screening also generally have universal vaccination programs including rubella, this viral infection is more frequent in countries without such screening. Accordingly, the antenatal ultrasound features of CRS are little known.

Objective

The diagnosis, management and outcome of rubella during pregnancy have been extensively reviewed elsewhere [2]. The goal of this review is to focus specifically on the

description of the signs of CRS accessible to prenatal diagnosis.

Materials and methods

We conducted a literature review with the Pubmed database. We searched for data concerning the prenatal period in antenatal or virological or pediatric literature, using the following keywords: “congenital rubella syndrome; rubella and pregnancy; fetal infection; congenital heart disease; and congenital cataract”. We have analyzed every case report and series in which there was a description of at least one case of CRS. The search covered the time period from the first cases described in 1941 to 2014, and after 1991 for the prenatal descriptions. We also analyzed every case reported to the French national reference center for rubella between 2011 and 2014.

We first present the results of the cases described antenatally and then the postnatal cases. We classified the postnatal abnormalities described according to their accessibility to antenatal diagnosis. As there is a risk of bias, we chose to present mainly absolute numbers, and to not calculate percentages, sensitivity or specificity or prenatal imaging. Finally, we discuss the most frequent ultrasound patterns encountered and thus to be looked for in cases with potential CRS.

Results

Antenatal descriptions

Between 1991 and 2014, 32 cases of CRS were diagnosed prenatally [4–11]. Every case was diagnosed during the first trimester after a maternal infection between 4 and 12 weeks of gestation. Seventeen of these 32 fetuses presented 56 different abnormalities detected before birth. Amniotic fluid anomalies in thirteen cases including: polyhydramnios in four cases, oligohydramnios in eight [4,6–8,11], and “foggy” amniotic fluid (which appeared to be meconium-stained, as meconium peritonitis was also observed) [9], IUGR (11/32 cases, 34%). Heart malformations (11/32, 34.3%) included ventricular septal defects (three cases) [11], atrial septal defects (two cases) [8,11], and aortic stenosis (one case) [11], total anomalous pulmonary venous return (one case) [4], axis deviation of the heart (one case) [4], tricuspid regurgitation (one case) [4], mitral valve abnormality (one case) (hyperechogenic focus) [5], and cardiomegaly (one case) [8]. Seven of 56 anomalies concerned the brain (12.5%): two with Dandy–Walker Syndrome [7,11], and one each with cerebellar vermis agenesis [4], hydrocephalus [11], ventriculomegaly [10], anencephaly [11], and periventricular calcifications [10]. There were two ocular abnormalities, each described in a single case (3% of all 32 fetuses): cataract [5] and microphthalmia [5]. There were 14 other ultrasound anomalies, including placentomegaly (5) [4,8], hepatosplenomegaly (2) [8,11], and one each of the following: a single umbilical artery 4, micrognathia 4, a short femur 4, ascites 8, a hyperechogenic bowel 8, and a hyperechogenic scrotal mass 9.

Postnatal description

We analyzed all postnatal signs reported in the literature in order to define the ultrasound features to look for when performing prenatal scans. There were 1970 abnormalities reported in 1109 children with CRS.

Ophthalmological abnormalities: There were 633 ophthalmological disorders described. Ultrasound abnormalities accessible to prenatal diagnosis are: cataracts 234/633 (37%) [4,6,7,12–27], microphthalmia 41 (6.5%) [4,6,12–14, 17,18,21,23,28]. Retinopathy 25 (4%) [26,29], chorioretinitis 178 (28%) [7,13,14,18,21,23,24,30,31], and glaucoma 25 (4%) [6,13,14,23,24] are not accessible to prenatal diagnosis.

Cardiac abnormalities: 427 cardiac abnormalities were described. Only 290 were clearly specified in the articles. Those that may be accessible to prenatal diagnosis were: pulmonary artery stenosis 81/290 (28%) [2,3,18,19,22,23, 26,27,32–35], septal defects 69/290 (23%) [3,4,6,7,12,14, 17–19,22,23,26,27,33,34,36,37], tetralogy of Fallot 5–290 (2%) [23,27], aortic stenosis 3/290 (1%) [6,23,27], aortic coarctation two cases [7,27], and one case of transposition of the great vessels [27], Ebstein’s anomaly [36], and pulmonary artery coarctation [23]. Patent ductus arteriosus 115/290 (39%) [3,4,6,7,12,14,17–19,27,28,30–34,36–38] is not accessible to prenatal diagnosis.

Brain abnormalities: Among the 126 cerebral abnormalities, 97/126 (78.5%) were microcephalies [2–4,7,13,15, 18,21,23,24,31,33,36–38], nine (7.5%) were hydrocephalus

[15,20,23], six (4.7%) [3,10,12,26,33] were cerebral calcifications, two anencephalies [20] and one case of cerebellar vermis agenesis [4], corpus callosum hypoplasia [4], and hydranencephaly [31]. All may be accessible to prenatal diagnosis.

Genitourinary disorders: There were 40/1970 genitourinary disorders. Abnormalities accessible to prenatal diagnosis were: three vesicoureteral reflux [23,28], two renal agenesis [20], and one case of hydronephrosis [23] and hypospadias [4]. Were not accessible to prenatal diagnosis: 18/40 (45%) ectopic testicles [12,23,9] (22.5%) inguinal hernias [23], 3 (7.5%) hydrocele [23].

Other abnormalities: 372 cases presented various abnormalities possibly accessible to prenatal diagnosis: 174 low birth weight [3–7,9,12–14,22,23,25,26,30–34,36,37,39], 55 cases of hepatosplenomegaly [7,9,12–14,16,18,22,25,31–33,36], 46 cases of purpura [13,14,16,18,22,24,25], 45 cases of thrombocytopenia [13,22,25], 10 long-bone anomalies [22], six micrognathia [22], four cases of syndactyly [18,22], and one each of umbilical vein dilation [32], duodenal stenosis [38], meconium peritonitis [9], cleft palate [18], and diaphragmatic hernia [20]. Hearing loss was reported in 375 children (19%) [3,6,7,12,13,18,20,23–27,31,28,29,39] and low birth weight in 174 (9%) [3–7,9,12–14,22,23,25,26,30–34,36,37,39].

During the period between 2011 and 2014, seven cases of CRS were reported to the French National Reference Center For Rubella (Hôpital Paul Brousse, Villejuif, France). Their antenatal anomalies included two cases of IUGR and one case of cataract, microphthalmia, a hyperechogenic point on the mitral valve, and a single umbilical artery. The postnatal abnormalities were four low birth weights, three neurological disorders (one psychomotor retardation, two undefined), two microcephalies, two hearing losses, two cataracts, one aortic coarctation, and one microphthalmia. Table 1 summarizes the reported morphological abnormalities in all 1148 prenatal and postnatal cases described in the literature accessible to prenatal diagnosis.

Discussion

Our investigations show the most frequent features that should be sought on ultrasound examination of fetuses with suspected CRS. We reviewed the data of 1141 cases of CRS published thus far, plus seven more cases that we describe here for the first time. We note that cases of antenatal CRS are rarely reported: only 32 cases. Most of the cases have been described in pediatric, virological, and neonatal studies, probably because most of the studies either come from countries without widespread antenatal ultrasound screening or preceded its development. For example, we found only one prenatal study published before 2000 [20]. We have not found many studies or case reports probably because many cases did not show original findings, and/or maybe because there were no authors willing to publish them. Moreover, the severity of the damage from infection in the first trimester of pregnancy might have resulted in the termination of some pregnancies before a thorough ultrasound screening because of the concerns of patients and/or practitioners.

Although the CRS was first described by an ophthalmologist, only one case with eye disease has been described before

Table 1. Anomalies accessible or not to prenatal diagnosis in cases of CRS (antenatal ± postnatal ± national reference center datas).

	Anomalies accessible to prenatal diagnosis		Anomalies not accessible to prenatal diagnosis
	>10 cases reported	<10 cases reported	
Heart	septal defects [2–4,6–8,14,17–19,22,23,26,27,33,34,36,37] (<i>n</i> = 74) pulmonary artery stenosis [2,18,19,22,23,26,27,32,34,35,38] (<i>n</i> = 81)	Aorta coarctation (<i>n</i> = 3), Aorta atresia (<i>n</i> = 3), transposition of the great arteries (<i>n</i> = 1), tetralogy of Fallot (<i>n</i> = 5), cardiomegaly (<i>n</i> = 1), pulmonary venous return anomalies (<i>n</i> = 1), axial heart deviation (<i>n</i> = 1), coarctation of the branches of the pulmonary artery (<i>n</i> = 1) [2,7,23,27] Ventriculomegaly (<i>n</i> = 10), Dandy-Walker syndrome (<i>n</i> = 2), anencephaly (<i>n</i> = 3), periventricular calcifications (<i>n</i> = 8), cerebellar vermis agenesis (<i>n</i> = 2), corpus callosum hypoplasia (<i>n</i> = 1), hydrancephaly (<i>n</i> = 1) [3,4,10,12,15,20,23,26,33] cleft palate (<i>n</i> = 1), low-inserted ears [18], micrognathia (<i>n</i> = 7) [4,22]	patent ductus arteriosus (<i>n</i> = 115) [3,4,6,7,12,14,17–19,27,28,30–34,36–38]
Brain	Microcephaly [2–4,7,13,15,18,23,24,31,33,36–38] (<i>n</i> = 99)		
Face	Cataract [4–7,12–27] (<i>n</i> = 237) microphthalmia [4,12–14,17,18,21,23,28] (<i>n</i> = 43)		Glaucoma (<i>n</i> = 25), Chorioretinitis (<i>n</i> = 178) [7,13,14,18,21,23,24,30,31], retinopathy (<i>n</i> = 25) [4,6,7,12–27]
Limbs			long-bone anomalies (<i>n</i> = 10) [22]
Genitourinary tract			ectopic testicle (<i>n</i> = 18) [9,12,23]
Abdomen	Hepatosplenomegaly (<i>n</i> = 57) [7,9,12–14,16,18,22,25,31–33,36]	Syndactyly (<i>n</i> = 4) [18,22] vesicoureteral reflux (<i>n</i> = 3), renal agenesis (<i>n</i> = 2), hydronephrosis (<i>n</i> = 1), hypospadias (<i>n</i> = 1) [4,12,23,28] Ascitis (<i>n</i> = 1) ⁶ , meconium peritonitis (<i>n</i> = 1), duodenal stenosis (<i>n</i> = 1), diaphragmatic hernia (<i>n</i> = 1) [9,18,20,38]	inguinal hernia [23]
Other	IUGR/Low birth weight (<i>n</i> = 189) [3–5,7–9,11–13,15,22,23,25,26,30–34,36,37,39] amniotic fluid abnormalities (<i>n</i> = 13) [4,7,8,11]		Purpura (<i>n</i> = 45), hearing-impairment (<i>n</i> = 347), thrombocytopenia (<i>n</i> = 45) [13,14,16,18,22,24,25]
Placenta		Placentomegaly (<i>n</i> = 5) [4,8] single umbilical artery (<i>n</i> = 2) ⁴	

birth [5]. As for other congenital infections, rubella virus may stay in the aqueous humor until adulthood [40]. The leading cause of congenital cataracts is idiopathic [41]. It is nonetheless likely that most ocular abnormalities were missed in the antenatal ultrasound examination, because these signs are frequently found in postnatal studies. A complete analysis of the fetus should aim to highlight ocular abnormality, by a meticulous examination of the eyes.

Our study allowed us to rank the signs suggestive of CRS that must be sought for in cases of known or suspected maternal infection. Because of the few available studies, the sensitivity and the specificity of ultrasound diagnosis of severe cases and sequelae has never been evaluated. If the infection occurs before 20 weeks of gestation, it is necessary to provide ultrasound monitoring twice a month to look for the major signs of infection we found in this review: IUGR, cerebral, ocular, and cardiac disorders. A thorough ocular analysis and echocardiographic follow-up are strongly recommended [4] and should be performed by an expert sonographer. If the infection occurs after 20 weeks of gestation, there is no risk of fetal malformation [29].

When a screening ultrasound performed during pregnancy finds the abnormalities listed here, CRS can be ruled out by analysis of maternal serology and/or amniotic fluid analysis [2].

The main limitation of our study is the heterogeneity of the studies we analyzed. The signs presented for each fetus were not always clearly specified one by one, so it was not possible to calculate the prevalence of each sign. No large studies have assessed prenatal descriptions of CRS. Since most studies have been published by virologists or pediatricians, we can only transpose pediatric anomalies to the fetus. Some studies focused specifically on cardiac or ocular disorders and ignored other abnormalities. Others included every child with in utero contact with rubella, regardless of gestational age at contact, so that most of the babies were born free of any clinical signs [20]. Still others, on the contrary, included only symptomatic cases [3,18,23,24]. The anomalies have not always been described with adequate precision. Some studies analyzed together the CRS cases confirmed by laboratory samples and those clinically suspected [18,22], while others analyzed them separately, consequently the prevalence of signs is inferior to the expected level for such a serious infection, and we presume that in some cases there was no actual infection of the fetus. There are also CRS cases diagnosed only many weeks after birth, for which it is impossible to know whether the clinical signs described were present at the fetal stage or if they appeared during the first days or months of life.

Even though rubella has become a rare disease in most developed countries, a lack of vaccination could lead to an outbreak and cause many public health problems such as CRS. For example, in Japan 11 000 cases of rubella appeared during the first semester of 2013 causing at least 13 confirmed CRS cases [42].

Conclusion

This extensive literature review shows that the ultrasound features of CRS are not well known, even though rubella was

the first teratogenic virus described. This review will help clinicians in the management of rubella during pregnancy by clarifying the findings to be sought.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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