Rubella

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Epidemiology

Rubella virus is transmitted person-to-person via infected respiratory droplets or, less commonly, from other sites such as urine, stool, and skin. Rubella circulates year-round, with a peak in winter and early spring; however, outbreaks are possible in crowded conditions (e.g., dormitories, barracks, cruise ships) or in populations where vaccine coverage is low [1].

Rubella virus has a basic reproduction number (R_0, the number of subsequent infections that result from a single infection in a homogenous population) of 5–7. This means that rubella vaccination coverage needs to be at least 80–86% to maintain effective herd immunity [2]. Data from National Health and Nutrition Examination Surveys shows that the proportion of US women with rubella immunity, defined as rubella antibody ≥10 IU, has steadily increased over the past 30 years (Fig. 1), since the inclusion of rubella vaccine as part of routine childhood immunization practice [3–5]. Ninety-four percent of kindergartners and 90% of adolescents surveyed during the 2016–2017 school year had received ≥2 doses of measles-mumps-rubella (MMR) vaccine; these rates have been relatively stable over the past decade [6, 7].

In 2015, the World Health Organization declared rubella and CRS eradicated in the Americas, as the incidence of CRS had dropped to <2 per 100,000 live births [8]. However, CRS remains common in other parts of the world, with an estimated incidence of 90–120 per 100,000 live births in Asia and Africa [9].

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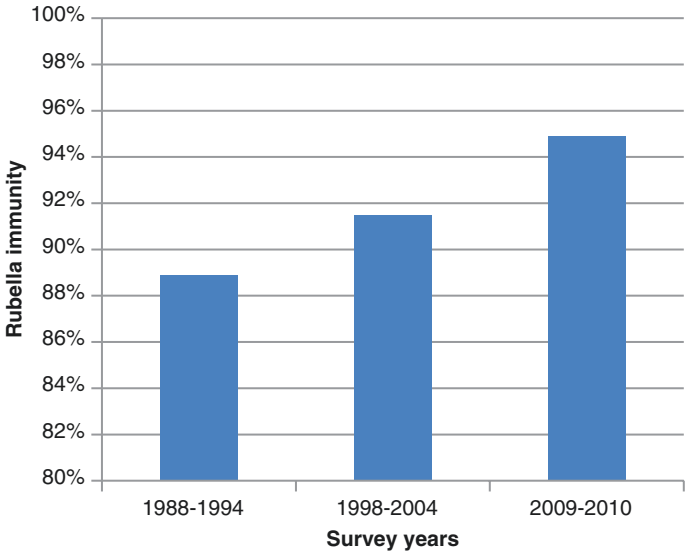

Fig. 1 Proportion of childbearing-age women who are rubella immune (≥10 IU) according to National Health and Nutrition Examination Survey data [3–5]. Women who are nonimmune should receive a single dose of rubella vaccine in the postpartum period or >28 days before becoming pregnant. Immunization during pregnancy is contraindicated

Pathogenesis

Congenital rubella syndrome has a similar pathogenesis to other congenital infections. Pregnant women with primary rubella infection have a period of viremia, during which time the virus can cross the placenta and reach the fetal circulation [10]. The probability of rubella virus crossing the placenta and the severity of fetal infection both decrease at later stages of pregnancy (Fig. 2) [11, 12]. For the purposes of this chapter, infants with signs of rubella infection are said to have CRS; infants with proven rubella infection but no clinical manifestations are said to be silently infected. These infants with clinically inapparent infections are more common—but less likely to be identified—than infants with CRS.

Clinical Findings

The classic triad of CRS includes congenital cataracts, cardiac defects, and sensorineural hearing loss (SNHL) [13]. However, most infants with in utero rubella infection are asymptomatic at birth but remain at risk for sequelae (e.g., hearing impairment) later in childhood.

Fig. 2 The risk of fetal loss and congenital rubella syndrome decreases markedly as gestation progresses. Fetuses of women infected in the first trimester are at highest risk due to ongoing organogenesis and eye development. Risk decreases after 10 weeks, and clinically apparent disease is unusual in infants infected after 20 weeks' gestation

Congenital Cataracts

Cataracts may be unilateral or bilateral and may be present at birth or develop over the first few weeks of life. Affected infants may also have microphthalmia. Fundoscopy may reveal focal areas of hyper- and hypopigmentation around the macula (the so-called "salt and pepper" retinopathy); this finding may be present even in the absence of cataract and is the most common ocular manifestation of CRS [14].

Congenital Heart Disease

Congenital heart disease occurs in the majority of infants with CRS. Patent ductus arteriosus is the most common lesion, followed by stenosis of the pulmonary valve or artery, aortic valve stenosis, coarctation, and tetralogy of Fallot. Atrial and ventricular septal defects seem to occur at the same rate in infants with and without CRS [15].

Sensorineural Hearing Loss

SNHL is the most common sequela of CRS and may be an isolated finding. Similar to congenital cytomegalovirus infection, CRS can cause unilateral or bilateral hearing loss, ranging from mild to profound, with onset in the newborn period or in later childhood [16].

Other Manifestations

CRS may present similarly to other congenital infections, with nonspecific signs of fetal infection such as intrauterine growth restriction, jaundice, hepatosplenomegaly, blueberry muffin spots, anemia, thrombocytopenia, and bony radiolucencies. However, these findings are nonspecific.

Diagnosis

Pregnant women: Pregnant women should undergo rubella antibody testing at their first prenatal visit. Generally, a titer of ≥10 IU is sufficient to provide immunity, although reinfection has been reported for women with low-level immunity (10–30 IU) [17, 18]. Pregnant women who are nonimmune or with low-level immunity who:

1. Have been exposed to an individual with a febrile exanthem
2. Develop a febrile exanthem

should be tested within 1–4 weeks for rubella and parvovirus (see chapter "Parvovirus") [19]. Identification of rubella IgM or IgG in a nonimmune woman, or ≥4-fold increase in IgG for a woman with low-level immunity (e.g., from 15 to 100 IU), is concerning for maternal infection (Fig. 3).

Fetus: For women with confirmed rubella infection during the first or early second trimester, amniocentesis, chorionic villus sampling, or fetal blood sampling allows direct testing of the fetus by PCR and can help inform decision-making discussions between the family and the perinatal care team [20].

Infants: Rubella virus is heavily excreted by infants with CRS and can be identified by culture or PCR from body fluids [21]. Rubella is most concentrated in the pharynx, but urine, conjunctivae, or cerebrospinal fluid can also be tested. Prompt, direct identification of the virus is the gold standard for diagnosis as it decreases the risk of confusing a postnatal infection with a congenital infection. Alternatively, serologic diagnosis is also possible either by identification of rubella IgM from the infant or by persistence of rubella IgG beyond 6–12 months of age, until such time as the child is immunized with measles-mumps-rubella vaccine [22].

Infants with probable or proven CRS should undergo thorough evaluation, including a complete physical examination and fundoscopy, echocardiogram, and baseline and follow-up audiologic evaluation.

Treatment

There is no effective antiviral therapy for CRS; treatment is supportive. Multidisciplinary follow-up care—including audiology, speech, occupational, and physical therapy—is required for infants with CRS in order to maximize their functional outcome [1].

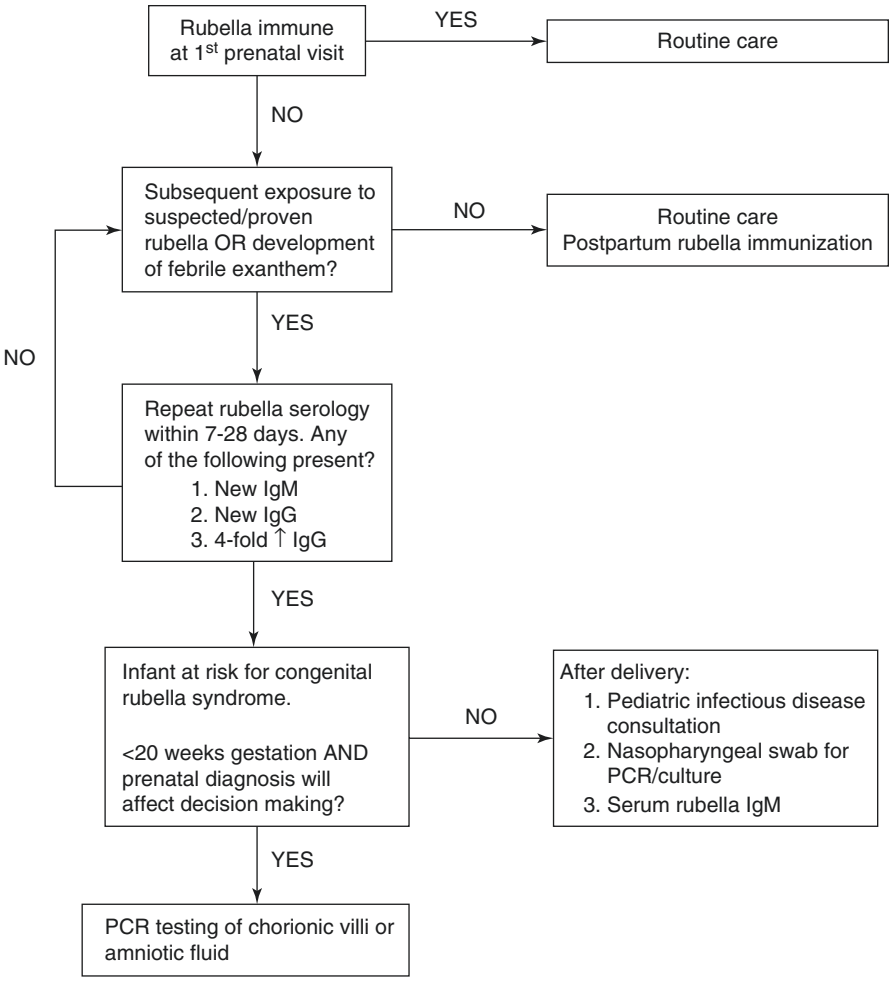

Fig. 3 Management approach to rubella nonimmune women and their infants during and after pregnancy

Prevention

Strategy: Active immunization with rubella-containing vaccines has virtually eliminated endemic rubella in the Western hemisphere. Immunization strategies in the United States include routine immunization with MMR at age 1 and 4 years as well as selective immunization for rubella nonimmune women of childbearing age.

Contraindications: MMR is composed of live-attenuated virus and is therefore contraindicated in pregnancy due to concerns for potential teratogenicity. It is also recommended that women avoid becoming pregnant for 28 days after receiving MMR [23]. However, there are no known cases of CRS following inadvertent

immunization of pregnant women with MMR vaccine. Therefore, women with undiagnosed pregnancy who receive MMR should receive routine antepartum care; pregnancy termination is not recommended [24]. Ideally, MMR should be given to nonimmune women during the immediate postpartum period [25, 26].

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