Congenital rubella syndrome—major review

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Abstract
Congenital rubella syndrome is a rare disorder with devastating ocular and systemic consequences. Although efforts to eradicate the disease have been in place for some time, some areas of the world continue to be affected by this disease. The burden of the disease weighs heavily on patients and society; therefore, vaccination and other preventative strategies should continue to be strongly encouraged.

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Congenital rubella syndrome (CRS) is a devastating consequence of rubella infection in pregnant women. Miscarriage, stillbirth, and a series of birth defects can be the sequelae of such infection, and widespread epidemics still exist in developing countries today despite massive worldwide vaccination efforts. Because this disease still places a significant burden on many countries (and people) around the globe, including the United States, preventive strategies are aimed to reduce rubella virus circulation, particularly among children and women of childbearing age. In this report, all aspects of congenital rubella syndrome are discussed, including its historical origins, risk of infection, vaccination, pathogenesis, general complications, ocular complications, diagnosis, and economic consequences.

Historical background of rubella and CRS

In 1752 and 1758, respectively, 2 German physicians, De Bergen and Orlow, discovered the modern day German measles, then known as Röthel.¹ It was not until 1866 that the name rubella was given to the disease by the Scottish physician Veale, who further elaborated on its clinical characteristics and significance.² About a century later in 1941, an Australian ophthalmologist, N. McAlister Gregg, observed that there was resounding evidence of pregnant mothers with rubella transmitting congenital defects to their offspring, including small size and birth weight and heart defects.³ His observations were the first record of the teratogenic effect of a viral infection.⁴,⁷ Gregg’s work was confirmed by the epidemiologists Swan et al.⁸,⁹ 2 years later, and they expanded Gregg’s observations, recording the associations of congenital heart disease, cataracts, deafness, the frequent presence of low birth weight, failure to thrive, and signs of meningitis with central nervous system damage. These clinical signs comprise all aspects of the modern-day congenital rubella syndrome.⁸,⁹

Since its discovery, rubella epidemics occur at 6- to 9-year intervals, and major pandemics have occurred every 10 to 30 years.⁶,¹⁰ The last major pandemic, the worldwide rubella epidemic of 1963 to 1965, infected an estimated 10% of all pregnant women, and 30% of infants from infected mothers ultimately manifested the congenital disease.¹¹ In the United States alone, there were at least 12.5 million cases of clinically acquired rubella with more than 13,000 fetal or early infant deaths, 20,000 infants born with major congenital defects, and 10,000 to 30,000 infants born with moderate to severe manifestations during the course of the epidemic.¹²⁻¹⁴ The eventual total cost of the rubella epidemic of 1963 to 1965 has been estimated at more than $2 billion.¹,¹⁵
Because of the magnitude and severity of fetal injury observed during this period, extensive study immediately took place after the last outbreak to determine what caused the disease and how it could be prevented. Active meningoencephalitis, liver, and spleen enlargement were predominant findings, and although live virus was discovered in almost every bodily organ, the virus was also found actively shedding in most bodily fluids and secretions. Infants were found manifesting forms of the fetal infection never previously recognized and in fact had chronic disease. It was a period of intense investigation into the rubella virus and its role as a human pathogen, and it was soon realized that rubella was an ideal model to illustrate the pathogenesis of fetal infection and the routes by which microorganisms can be transmitted from maternal to fetal systems.9

In 1969, the rubella virus was isolated and identified as the specific organism responsible for the exanthematous disease and the devastating effects of intrauterine infection on the fetus.8,12,13,16-19 The first vaccine was licensed in the United States that same year, and since then the reduction in congenital infection from rubella has been dramatic and long standing.1,9,20,21

Rubella’s virtual eradication in populations with effective and universal immunization programs is a major achievement of medical science. However, despite the United States’ extensive vaccination program, there is still persistent rubella infection and CRS even with high coverage of individuals with the vaccine. Religious communities that refuse vaccination, immigrant women, and institutionalized persons are a few of the sources of continued infection in the United States today.22,23 Additionally, sporadic cases of CRS will continue to occur because of lack of universal immunization, primary or secondary vaccine failure, and reinfections.22,23 Since its inception, much knowledge has been gained about the gestational effects of rubella, and now there is an understanding that there are other direct effects on fetal development, including miscarriage and stillbirths; in addition, it is now recognized that not all effects of CRS are seen at birth.24

Epidemiology of CRS

The absolute risk of CRS among children born to mothers infected during pregnancy varies greatly depending on the study, ranging from 1.7 per 1,000 live births in Israel, 0.7 in Oman, 2.2 in Panama, 1.5 in Singapore, and 1.7 in Jamaica.25 Rubella is a worldwide disease, with peak age incidence less than 10 years of age, causing 70% to 90% of the adult population to have been introduced to the disease with those individuals now possessing rubella antibodies. However, vaccination is still extremely important and has significantly reduced the prevalence of both rubella infection and CRS.25,26

The United States and most Western countries have introduced a dual strategy vaccination against rubella: all infants 12 months to 15 months of age are now vaccinated, and there is selective vaccination of susceptible women of childbearing age.25 Currently, in the United States, the RA 27/3 rubella vaccine is available as a single-antigen preparation, or combined with the mumps vaccine, or combined with the measles and mumps vaccines as MMR (MMRII; Merck & Co., Inc., West Point, Pennsylvania), or combined with the mumps, rubella, and varicella vaccine as MMRV (ProQuad; Merck & Co., Inc., Whitehouse Station, New Jersey).27 These vaccinations have left seropositivity rates of more than 95% in the adult population, and currently the estimated incidence of CRS is less than 2 per 100,000 live births.22,25,26,28 The vaccine has a seroconversion in more than 95%, and the rubella antibody persists long term, substantiating the idea that the vaccine is very efficacious.22,25,29,30 Today, it is believed that 10% to 20% of postpubescent individuals are still susceptible to rubella in developed countries, and up to 68% are susceptible in developing countries, allowing for the continued transmission of rubella virus among women in reproductive age groups.24,31,32

In the prevaccine era, rubella was most common in children ages 5 through 9, with 85% of individuals having immunity by ages 15 to 19 and almost 100% by ages 35 to 40.24,33 These rates are similar to those of the prevaccine era in industrialized countries.31,34 Today, there are an estimated 238,000 children born worldwide with CRS each year, mostly in developing countries.35 From 1969 to 1989, the annual reported cases of rubella in the United States decreased 99.6%, and the number of reported cases of CRS decreased 97.4%.36 After a slight resurgence in the United States during 1990 and 1991, the number of reported rubella cases reached record lows during 1992 through 1996 with an annual average of 183 cases.36 In 2000, there were 192 reported cases of rubella in the United States, and between 1997 and 2000 there were only 30 reported infants born with CRS.37,38

The epidemiologic profile of rubella in the United States has changed dramatically since the 1990s, including shifts in the age distribution, ethnicity, country of origin of patients, and in the setting of outbreaks. During the early 1990s, most rubella cases in the United States occurred among persons age less than 15 years; since the mid-1990s, persons age 15 years or older have accounted for most reported cases. In 1999, adults accounted for 86% of cases, an increase from 41% in 1990, and 73% of persons with rubella were Hispanic, compared with 4% in 1991.39 Most of these persons were foreign born. In recent rubella outbreaks, most cases occurred among persons from Mexico and Central America. Moreover, outbreaks predominantly occurred in workplaces and secular communities: before the mid-1990s, outbreaks occurred mainly in religious communities, schools, jails, and other closed environments. Recently, rubella outbreaks have been identified in poultry and meat processing plants that employ large numbers of foreign-born workers.39

The number of cases of CRS has also declined in the United States and now disproportionately affects infants born to foreign-born women. During 1997 to 1999, a total of 81% of infants reported with CRS were Hispanic, and
92% were born to foreign-born mothers. Although information on country of origin was not collected in 1991, 19% of all infants with CRS were Hispanic. Today, 78 countries have a national policy of rubella vaccination. The rubella vaccine is currently used in 92% of industrialized countries and 28% of developing countries.

**Pathogenesis of CRS**

The significance of rubella derives from its teratogenic effects on the fetus when rubella affects pregnant women. The rubella virus is a member of the togavirus family, and the genus, *Rubivirus*. It is closely related to alphaviruses but differs in that it is not transmitted by vectors. The rubella virus is roughly spherical with a diameter of 60 to 70 nm. It is composed of an icosahedral nucleocapsid containing a single-stranded RNA genome; this is surrounded by a complex lipid envelope. The rubella virus multiplies in the lining of the respiratory tract or in local lymph nodes before passing into the bloodstream and spreading throughout the rest of the body.

Typically, rubella infection after birth is subclinical and occurs 14 to 21 days after exposure to the virus. Transmission is spread by droplet. In pregnant women, the rubella virus can infect and replicate in the placenta. The outcome of fetal infection is dependent on the gestational timing of maternal rubella, but fetal infection can occur at any stage of pregnancy.

The risk of fetal infection varies according to the time of onset of maternal infection. Infection rates are highest during the first trimester (81% overall with 100% infection rate in weeks 1 through 10), declining to a minimum of 25% at the end of the second trimester, and rising back to 100% during the last month. Although a fetus becomes infected with the virus, malformation will not necessarily develop. The estimated risk for malformations is 90% for those infected in weeks 2 through 10, 34% for those infected in weeks 11 through 18, and no malformations for those infected after 18 weeks. However, in one prospective study of 1,016 confirmed rubella cases in pregnant women, only 407 (40%) continued their pregnancy to term.

The mechanisms by which the rubella virus causes fetal damage are poorly understood. Before the development of the maternal immune response, the virus spreads through the bloodstream and may affect multiple maternal tissues, including the placenta. As a result of placental damage, the virus frequently will cross the placenta into the fetus. Once inside the placenta, the fetus undergoes a cellular deficiency that causes disturbances of organogenesis, which is limited to the critical first 12 weeks of development.

During this first trimester, the fetus is incapable of a normal immune response and instead relies on maternal immunoglobulin G (IgG) antibodies transferred from the mother across the placenta. Unfortunately, at this early stage of development, placental transfer appears to be inefficient, and fetal blood levels of IgG are only 5% to 10% of those in maternal serum. It is not until after the first trimester that serum IgG levels increase and eventually at term may even exceed those of the mother.

During the second trimester and beyond, changes to the placenta are thought to decrease the risk of fetal infection significantly more than the enhanced fetal immune response, and, as previously mentioned, infection and malformation risk decreases dramatically during this period. Thus, as the fetus progressively matures and starts to produce its own antibodies, it begins to develop the ability to launch both a humeral and cytotoxic response to the rubella virus. With the combination of its own antibodies and the continued transferred maternal IgG to the fetus, the fetus can largely protect itself from viral damage for the remainder of gestation, although it is incapable of getting rid of the virus completely.

The rubella virus is generally noncytolytic, allowing cell survival but resulting in persistently infected cells with a decreased growth rate and shortened survival time. Infected cells have reduced mitotic activity as a result of chromosomal breakdown and through the production of a protein that inhibits mitosis. Focal cytolysis secondary to infection of cells with the rubella virus can be found in many organs, but inflammation is not a predominant feature of congenital rubella. All of these changes, occurring at the cellular level, suggest that sufficient cell mass does not accumulate to shape embryonic parts normally, and the required minimum number of replicative cell cycles for the embryo to develop properly does not occur.

The major manifestations and the delayed manifestations of congenital rubella are caused by tissue destruction and scarring. This may be caused by viral persistence with resultant ongoing damage, immune mechanisms such as autoimmunity circulating rubella-specific immune complexes or defective cytotoxic effector cell function.

The rubella virus in CRS can be very persistent. Rubella virus particles may be retained in secluded sites such as the crystalline lens, and virus antigens are believed to persist in various target organs where they can undergo recurrent periods of increased virus production and replication. The rubella virus can be isolated from the cerebrospinal fluid in one third of all patients and has been detected in the urine, stools, and nasopharyngeal secretions in all CRS infants; the virus may persist for up to 1 year of age in severely affected infants. In one instance, the virus has been isolated in a 28-year-old man with CRS.

Fetal infection risk is greatest after primary infection of the mother, although reinfection is now known to cause CRS despite serologically proven immunity. The risk of CRS after reinfection is believed to be between 5% and 8%, mainly during the first trimester, although there are increasing numbers of reports of CRS after reinfection in mothers, even in those who have been shown previously to have serologically proven immunity. However, in these few reported cases of reinfection with a confirmed diagnosis of CRS, the disease is seldom teratogenic, and
although reinfection is not uncommon (>50% in the vaccine-immune patient and 5% in the naturally immune patient), it is almost always subclinical.25,50,51

Systemic manifestations

The term congenital rubella syndrome is used, as defined by South and Sever,15 to denote any combination of the findings known to result from gestational rubella. The classic CRS is characterized by the combination of cardiac, ocular, and hearing defects, although the active rubella virus in a fetus can infect virtually any organ. As many as 50% of CRS infants will appear normal at birth, but abnormalities of the central nervous system may develop with time.25,51 The main defects of the disease (listed in order of decreasing frequency) are deafness, mental retardation, cardiovascular defects, and ocular defects; however, thrombocytopenia, hepatitis, myocarditis, bone lesions, dental defects, hypospadias, cryptorchidism, inguinal hernia, interstitial pneumonitis, meningoencephalitis, cerebral calcification, nephrosclerosis, nephrocalcinosis, splenic fibrosis, diabetes mellitus, thyroid dysfunction, and a rare neurodegenerative disorder (panencephalitis) have been reported.46,47,53-55 Chemical changes on a cellular level secondary to an autoimmune response, immune-mediated cell destruction, and prenatal damage may account for these late-onset manifestations.47,56-59 Therefore, congenital rubella should be viewed as a chronic disease capable of producing ongoing vital organ damage throughout life.

By spreading through the vascular system, the first organs targeted (usually receiving lethal damage) are the heart and blood vessels. These organs are affected only after infection of the fetus in its first trimester; cardiovascular and other vascular anomalies are rare afterward.15

The worst damage from rubella seems to be caused by vascular hypoxia secondary to the rubella infection of endothelial cells. Damaged endothelial cells can act as a source of virus-infected emboli and lead to small blood vessel thrombosis.60

When the heart is targeted, there is direct viral damage to the myocardium, affecting primarily the left atrium and the heart septa, leading to thrombosis, necrosis, and hemorrhage.47 Ultimately, patent ductus arteriosus associated with infection and stenosis of the pulmonary artery and its branches usually are the cause of fetal termination.

Diffuse intimal changes in the pulmonary and systemic arteries of large and medium-sized arteries are also affected in fetuses infected during the first trimester, and in some cases this proliferation can be severe enough to occlude the vessel, leading to pulmonary stenosis and ischemic necrosis of adjacent tissue.24 However, it appears that beginning from the second trimester and beyond, maternal IgG limits cardiovascular and systemic vascular damage and protects the fetus from these anomalies later in development.47

A fetus infected with CRS during a later stage in pregnancy often exhibits a slowed growth rate during preschool years, and the head circumference often is smaller than that of age-matched controls (this second anomaly is typically associated with congenital cataracts as well).24 Delayed manifestation of CRS underscores the importance of careful follow-up of these patients, because the altered immune system of CRS patients allows complications to take place later in life.24,25 As many as 5% of individuals with CRS have some form of thyroid disease starting in their teenage years, upward of 20% have diabetes by age 35, and, although rare, rubella panencephalitis is an ultimately fatal but very rare delayed manifestation of CRS.24,57 Sever et al57 have shown that individuals born with congenital rubella infection only, and not CRS at birth or in early infant life, have been unaffected, but long-term follow-up of this group is currently unavailable, and therefore the risk of complications remains unknown.57

Ocular manifestations

The fetal eye commonly is affected via the bloodstream, although the lymphatic system may also play a minor role in infection transmission.9,61 Because the fetus does not have cell-mediated or humoral immune defenses until around the 20th week of gestation, the rubella virus can pass virtually unchallenged via the capillary network to every part of the developing eye.9 The ocular pathologies most commonly observed with CRS are nuclear cataracts, microphthalmia, and pigmentary retinopathy. These ocular defects often evolve over time and progress mainly after birth.

Rubella cataract is the most common ocular complication of CRS. As rubella infects the embryonic lens, it slows cell division and maturation. This alteration during the growth of the lens causes the lens fibers to degenerate, fail to dehydrate, and eventually become opaque. There is a central area of degenerate lens fibers that do not incorporate amino acids into new protein and therefore do not contain any intracellular organelles.62 Transparent secondary lens fibers then cover the core of opaque embryonic lens fibers.

For a cataract to form because of rubella, the mother must have contracted the virus before the ninth to eleventh week of pregnancy.52,62 Often, the cataract is unilateral, because 1 embryonic eye may develop somewhat faster than the companion eye, and because the rubella infection of the lens has a narrow interval of vulnerability. It is possible that the virus could entirely miss infecting 1 eye by reaching that eye hours or days later than the affected eye.62 Progression of the cataract can take place after birth because the young lens can act as a reservoir for the virus. In addition, spontaneous partial or complete resorption of the cataract has been described after rubella infection.63,64
Microphthalmos is another frequently seen sequelae of CRS. The condition exists clinically if the newborn’s eye is less than 16.6 mm in diameter. It can be either unilateral or bilateral and is often linked with a cataract. Microphthalmos has been reported in an estimated 10% to 20% of all children with CRS and appears to be relatively mild in most cases, with extreme microphthalmos being rare. The delay in the maturation process of the eye on a cellular level is the presumed cause of the abnormality, and many think that the generalized slowing of replication commonly seen in rubella-infected cells results in an ocular “failure to thrive.” Although microphthalmos itself is not a cause of decreased vision, these eyes often have coexisting nystagmus, cataracts, and retinopathy, ultimately limiting vision. If microphthalmos is associated with a bilateral cataract, the postoperative prognosis generally is poor.

Pigmentary retinopathy is also a common ocular abnormality associated with CRS. It is traditionally characterized by a salt and pepper fundus appearance and was originally described by Gregg as “a piece of coarse Scotch tweed used for a sportscoat over which pepper had been thrown.” The retinopathy may be unilateral or bilateral, central or peripheral, irregularly distributed, mild, or marked. The pigment deposits may vary from fine, sprinkled, or granular shapes throughout the retina and sometimes appear similar to retinitis pigmentosa. Although the pigmentary changes can occur anywhere in the retina, they are more commonly located at the posterior pole. It occurs in approximately 40% to 60% of all cases of CRS but has been reported variably from 13.3% to 61%. The pigmentary changes take place because of focal atrophy and pigment alterations of the retinal pigment epithelium with an otherwise normal retina and choroids.

Initially thought to be a stationary disease (most cases of retinopathy develop or progress in infancy and regress in adult life), recent evidence suggests that, although rare, the pigmentary retinopathy actually can progress throughout life. Patients with retinopathy usually enjoy relatively good visual acuity into adulthood, but a sudden loss of vision secondary to subretinal neovascularization can occur. Eleven cases have been previously reported with onset between 9 and 19 years of age, with 8 of those individuals having severe central vision loss. Photodynamic therapy may be an effective treatment for subfoveal choroidal neovascularization secondary to rubella retinopathy, as one study indicates an improvement of visual acuity from 20/200 to 20/60 after such treatment.

Without identifiable neovascularization, vision remains decent even with the retinopathy; individuals rarely present with worse than 20/60 acuity without secondary complications and, more commonly than not, vision is completely unaffected. In addition, peripheral vision typically is normal, as are electrophysiologic test results that distinguish CRS retinopathy from other similar masqueraders such as retinitis pigmentosa, X-linked ocular albinism, and toxic diseases of the retinal pigment epithelium.

Glaucoma has also been a well-described complication of CRS, either congenital or acquired. The congenital glaucoma associated with CRS is thought to be an isolated anomaly typically seen in newborns with bupthalmos and corneal haze. Failure of absorption of the mesoderm of the angle or failure of the canal of Schlemm to differentiate is the cause of this congenital abnormality. It is rarely associated with cataracts or microphthalmos.

Alternatively, secondary glaucomas tend to occur in severely damaged eyes with microphthalmos and cataracts, generally developing in the second decade of life and carrying a very poor visual prognosis. The presence of glaucoma may be very difficult to diagnose in these individuals because of systemic abnormalities and disabilities, nystagmus, and the presence of small rigid pupils obstructing a clear view of the optic nerve. It is presumed that a form of trabeculodysgenesis or persistent viral damage to the trabeculum is the etiology of glaucoma in these individuals. However, there is also a belief that some secondary glaucomas develop in individuals with concurrent CRS and chronic uveitis as well. This can occur in individuals with CRS, typically after cataract surgery. These eyes will tend to present with only minimal signs and symptoms of a uveitis, and a detailed slit lamp examination may show only mild evidence of inflammation with few keratic precipitates and only a minimal anterior chamber reaction. The incidence of glaucoma varies in CRS from 2% to 15% depending on the study.

Glaucoma also can cause corneal changes. The most common corneal problem is corneal haze, typically remaining and associated with visual acuity of 20/200 or worse if present at birth, although some cases have resolved spontaneously by age 1. In addition, corneal hydrops and keratoconus have also been described, but these cases have all been associated with mental retardation and are thought to be secondary to the independent mannerisms (constant eye rubbing) rather than to the disease itself.

Strabismus is another finding associated with CRS. The deviation occurs frequently as a sequelae to organic amblyopia secondary to microphthalmos, cataract, or glaucoma and tends to occur more frequently in concert with individuals with cerebral palsy. Typically, the strabismus is an esotropic deviation, and for the most part, surgical repair results in little improvement. Strabismus is 4 times more common in individuals with CRS, and although esotropia is more common, exotropia may also be seen. In addition to strabismus, latent, fine-amplitude, and jerk nystagmus may also be seen in individuals with CRS.

Hyperopia is much more common in individuals with CRS than myopia, which is uncommon. The smaller and shorter eyes in these individuals accounts for this phenomenon. In one older study, the hyperopic refractive error averaged +2.30 diopters.

Poor development of the dilator muscles of the iris can lead to iris atrophy in some individuals with CRS. This often explains why pupil dilation is difficult to achieve in individuals with CRS and how this anomaly can make cataract surgery more difficult.
Because of the increased incidence of diabetes secondary to CRS later in life, diabetic retinopathy is also increasing in frequency in these individuals and therefore must be monitored. Other complications secondary to CRS that may occur include iris and uveal colobomas and aphakia.

**Diagnosis of rubella during pregnancy**

In women affected with rubella during pregnancy, a prenatal diagnosis of a rubella-infected fetus may be beneficial. However, counseling of these women may be difficult because the rate of CRS is always lower than that of the maternal infection rate and because not every infection leads to fetal damage.

There are 2 accepted forms of early diagnosis, amniocentesis and fetal blood testing. Both tests should be performed 6 to 8 weeks after maternal infection but yield the best reliability if the fetus is at least 22 weeks old. The first method is a reverse-transcriptase polymerase chain reaction (RT-PCR) on amniotic fluid for rubella virus, which in 1 study showed a sensitivity and specificity of 100%. It concluded that amniotic fluid was the most suitable clinical specimen for diagnosing fetal rubella virus infection. Although this is still held to be true, there have been cases in which the rubella viral infection of a fetus was not detected using this method, leading some to believe that fetal blood should be tested for specific rubella immunoglobulin M antibodies. Either way, it is important for families to understand that these tests are for the detection of maternal and fetal infection only and cannot indicate the type or level of fetal damage.

**Economic consequences**

The rubella vaccination program in the United States has resulted in a significant reduction of morbidity and mortality and in cost savings over time. In the United States alone, the lifetime cost of treating a patient with CRS is estimated at more than $200,000. In other countries, the cost varies, from $63,900 in Guyana, about $50,000 in Barbados, and approximately $14,000 in Jamaica. It cost varies, from $63,900 in Guyana, about $50,000 in Barbados, and approximately $14,000 in Jamaica. The cost effectiveness of a mass vaccination campaign is estimated to be at least $2,900 per case of CRS prevented.

The initiative of countries around the globe to eradicate rubella has provided vital information on the successful implementation of mass vaccination campaigns for millions of people and on the cost-benefit of immunizing against rubella infection. As countries weigh the relative costs of including vaccination against the economic burden of caring for its citizens with CRS, cost-benefit analysis becomes a paramount issue. To date, the benefits of vaccination far outweigh the costs associated with the treatment and rehabilitation of children and adults with CRS.

**Conclusion**

Congenital rubella syndrome is a devastating condition that has multiple consequences for any society, both medical and financial. As such, the implications of this disease are imperative for clinicians and politicians alike to comprehend. To date, preventative strategies have made large differences, but there is still much more work to be done.

**References**


