

Congenital Rubella Syndrome (CRS) ^[1]

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Congenital rubella syndrome (CRS) can occur in children whose mothers contract the rubella virus, sometimes called German measles, during [pregnancy](#) ^[2]. Depending on the gestational period when the mother contracts rubella, an infant born with CRS may be unaffected by the virus or it may have severe developmental defects. The most severe effects of the virus on fetal development occur when the mother contracts rubella between [conception](#) ^[3] and the first [trimester](#) ^[4]. Defects from maternal rubella in the first [trimester](#) ^[4] are included in the term congenital rubella syndrome, but physicians and researchers specifically refer to those defects as rubella embryopathy. Developmental defects are less severe if the mother contracts rubella in the second [trimester](#) ^[4], and they are generally negligible if the infection occurs in the third [trimester](#) ^[4]. Prenatal rubella infection can cause [birth defects](#) ^[5] which include deafness, compromised vision, abnormal heart development, and damage to the [central nervous system](#) ^[6] which can lead to compromised cognition and learning disabilities.

Rubella was one of the first viruses classified as a teratogen, a classification that introduced the possibility that environmental agents such as viruses could cause [birth defects](#) ^[5] during embryological and fetal development. Norman McAllister Gregg, an ophthalmologist in Sydney, Australia, noted a correlation between maternal rubella infections and damage to developing fetuses in 1941. In the wake of a rubella epidemic in Australia, Gregg noted an increase in the number of children treated for congenital cataracts, with seventy-eight children treated for congenital cataracts in 1940. The mothers of sixty-eight of those children had contracted rubella in the first [trimester](#) ^[4] of [pregnancy](#) ^[2]. Gregg speculated that the rubella virus caused [birth defects](#) ^[5], and he published "Congenital Cataracts Following German Measles in the Mother" in 1941. Although many at the time questioned the possibility of environmental toxins passing from pregnant women to fetuses and causing [birth defects](#) ^[5], Gregg and fellow researchers continued to investigate the rubella connection. With the support of epidemiologists, Gregg showed that maternal infections caused developmental defects. His publication of "Further Observations on Congenital Defects in Infants Following Maternal Rubella" in 1944 outlined the trio of [birth defects](#) ^[5] that then defined CRS: deafness, visual impairment, and heart defects.

In contrast to CRS, rubella is a mild viral infection passed from person to person through droplets spread when people with rubella cough, sneeze, or talk. The symptoms of rubella are generally mild to non-existent in children, but they become more severe when contracted in later adulthood. The rubella virus incubates during the first two weeks following infection, and it is communicable between the first and second week when it is still asymptomatic. The symptoms of rubella infection follow the incubation period and are at times mistaken for the flu, as symptoms include fever, joint pain, headache, and swollen lymph nodes. As the word rubella is Latin for little red, rubella can also be accompanied by its namesake spotted red rash, which starts on the faces of affected individuals and can spread down the length of their torsos. Rubella can cross the [placenta](#) ^[7] from an infected pregnant woman to her developing embryo or [fetus](#) ^[8] after the first week of incubation. The virus remains in the fetal blood stream for the remainder of the [pregnancy](#) ^[2], and infants born with CRS can secrete the virus after birth, potentially infecting other infants and un-vaccinated adults.

Rubella infection can cause developmental defects in the developing embryo and [fetus](#) ^[8], which are more severe when the mother contracts rubella in the first [trimester](#) ^[4] compared to later in [gestation](#) ^[9]. The range in severity of CRS defects results from several factors, such as the sensitivity of the embryo to teratogenic effects, the transfer of maternal antibodies to the [fetus](#) ^[8] as [gestation](#) ^[9] progresses, and the increase in fetal immunological responses as the [pregnancy](#) ^[2] progresses. Researchers study how the virus damages infected cells in experiments with animal models: [rhesus macaques](#) ^[10], [rabbits](#) ^[11], and [rats](#) ^[12], among others. Scientists' results indicate that the virus shortens the cell life cycle and increases premature cell death ([apoptosis](#) ^[13]) compared to non-infected cells. The [birth defects](#) ^[5] of CRS occur because the rubella virus impacts certain cell populations during development. Increased cell death may also cause many affected fetuses and infants to be born with lower birth weights (intrauterine growth restrictions) than the gestational norms.

Developmental abnormalities of CRS include ocular, auditory, and cardiovascular defects, [central nervous system](#) ^[6] disorders, and other organ-related defects. A woman who contracts rubella prior to [conception](#) ^[3] or during the first [trimester](#) ^[4], also increases her risk of [miscarriage](#) ^[14] and stillbirth. Impaired vision and hearing are the most common [birth defects](#) ^[5] resulting from CRS, and can include cataracts in one or both eyes, abnormally small eyes (microphthalmia), glaucoma, retinal degeneration, and uni- or bilateral deafness.

The virus can also cause congenital cardiovascular defects which impact the flow or oxygenation of the blood supply in the [fetus](#)^[8]. One common abnormality is a ventricular septum defect, which is a hole in the septum or wall separating the left and right ventricles of the heart. Another common defect of rubella infection is patent ductus arteriosus which is the persistence of a blood vessel from the pulmonary artery to the aorta that allows fetal blood to bypass the lungs during the fetal stage, but is normally sealed upon birth. CRS may also cause pulmonary valve stenosis, an abnormal narrowing of the valve connected to the pulmonary artery, which directs blood to the lungs for oxygenation.

Other CRS-related developmental abnormalities include damage to the [central nervous system](#)^[6], and organ damage that can include thyroid, spleen, liver, and bone marrow defects. Further, congenital rubella infections can cause an overall decrease in the amount of [gray matter](#)^[15] in the brain, which can lead to an abnormally small head ([microcephaly](#)^[16]), developmental disabilities, and motor coordination or speech delays. Enlargement of the spleen and liver can also occur, which results in bone lesions exacerbated by low platelet counts (thrombocytopenia) in affected infants.

While rubella is particularly damaging to the developing embryo during the first [trimester](#)^[4] of [pregnancy](#)^[2], maternal infection does not always indicate that the child will be born with the developmental defects most commonly associated with CRS. Physicians often recommend prenatal counseling and laboratory assessments. The laboratory tests can include ultrasounds and sampling the amniotic fluid (amniocentesis), fetal blood (cordocentesis), or placental tissue (chorionic villus sampling) for the antibodies associated with rubella infection (Immunoglobulin G and Immunoglobulin M). Ultrasounds are the least invasive test to the pregnant woman and the [fetus](#)^[8], but they are also the least informative of all the tests, and are generally used to assess intrauterine growth restrictions and major morphological defects. The remaining fetal and maternal tissue tests are more invasive, but offer more accurate assessments of the risk that prenatal rubella infection poses to developing fetuses.

As rubella is a virus, there are no specific treatments to cure rubella or mitigate the effects of CRS on prenatal development. Instead, physicians and public health workers focus on the prevention of rubella infections across all demographics, not just pregnant women or women of reproductive age. Scientists isolated the rubella virus in 1961, and Stanley Plotkin at the Wistar Institute in Philadelphia, Pennsylvania, created the first rubella vaccine in 1966. Before rigorous vaccination programs began in developed nations, rubella epidemics were frequent and CRS was a major cause of [birth defects](#)^[5]. The US Centers for Disease Control and Prevention reports a total of 20,000 cases of CRS between 1962 and 1965, compared to four infants born with CRS between 2001 and 2004. Cases of congenital rubella also decreased in the same time period, from 57,686 reported infections in 1969 to only nine individuals in 2004.

Based on the decrease in rubella cases and CRS, the US Centers for Disease Control and Prevention announced in 2005 that rubella and CRS has effectively been eliminated in the US as of 2004, as adults that contracted rubella or gave birth to CRS-affected infants in the US generally came from countries that lacked rigorous rubella vaccination programs. Additionally, the World Health Organization reported that all developed countries as of 2010 include rubella vaccination as a component of their immunization programs. However, lower vaccination rates exist in areas of South America, Africa, and Southeast Asia, where CRS and rubella persisted as epidemiological concerns.

Sources

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measles, during pregnancy. Depending on the gestational period when the mother contracts rubella, an infant born with CRS may be unaffected by the virus or it may have severe developmental defects. The most severe effects of the virus on fetal development occur when the mother contracts rubella between conception and the first trimester. Defects from maternal rubella in the first trimester are included in the term congenital rubella syndrome, but physicians and researchers specifically refer to those defects as rubella embryopathy. Developmental defects are less severe if the mother contracts rubella in the second trimester, and they are generally negligible if the infection occurs in the third trimester. Prenatal rubella infection can cause birth defects which include deafness, compromised vision, abnormal heart development, and damage to the central nervous system which can lead to compromised cognition and learning disabilities.

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