REVIEW

Rubella and pregnancy: diagnosis, management and outcomes

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ABSTRACT
Rubella is a mild viral disease that typically occurs in childhood. Rubella infection during pregnancy causes congenital rubella syndrome, including the classic triad of cataracts, cardiac abnormalities and sensorineural deafness. Highly effective vaccines have been developed since 1969, and vaccination campaigns have been established in many countries. Although there has been progress, the prevention and diagnosis of rubella remain problematic. This article reviews the implications and management of rubella during pregnancy. © 2014 John Wiley & Sons, Ltd.

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INTRODUCTION
Rubella is a mild viral disease that typically occurs in childhood. In 1941, an Australian ophthalmologist, Norman McAlister Gregg, established the relationship between congenital defects and rubella during pregnancy, thus demonstrating the teratogenic potential of the rubella virus.[1] Rubella easily crosses the placenta of infected pregnant women; in the first trimester, rubella causes miscarriage or fetal death, or congenital rubella syndrome (CRS) could develop. CRS includes auditory, sensorineural, cardiac and ocular abnormalities. In cases in which the primary rubella infection occurs during the first 4 months of pregnancy, a prenatal diagnosis of fetal infection could be proposed. Although progress has been made, the prenatal diagnosis of rubella is not always easy. The incidence of rubella has significantly decreased in many countries because of vaccination campaigns; however, rubella has not disappeared in developed countries and is a significant source of disability.

This article reviews the implications and management of rubella occurring during pregnancy.

THE VIRUS
The rubella virus belongs to the Togaviridae family and is an enveloped, positive single-stranded RNA virus, with a 9.8-kb nucleotide length. The viral genome encodes five proteins, two non-structural proteins (p90 and p150) and three structural proteins (two glycoproteins, E1 and E2 and the capsid protein).[2] The E1 glycoprotein contains the antigenic determinants that induce major immune responses and a hemagglutination-inhibiting and hemagglutination-neutralizing epitope.[3,4]

A single serotype of the wild-type virus and several genotypes circulate globally.[5] In 2005, the World Health Organization (WHO) defined a minimal acceptable window of 739 nucleotides (8731–9469) within the E1 gene to identify the genotypes. On the basis of this partial E1 gene sequence, the genotypes are divided into two major phylogenetic groups, clades 1 and 2, which differ by 8% to 10% in their nucleotide sequences. Twelve genotypes (1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, 1J, 2A, 2B and 2C) and one provisional genotype (1a) of rubella virus are recognized. Some are widely distributed (1E, 1G, 1J and 2B), and others are geographically restricted, occurring sporadically.[6,7]

PATHOGENICITY AND EPIDEMIOLOGY
Before the vaccination era, and in countries that have not implemented rubella vaccination, rubella has typically occurred in the spring, with sporadic cases appearing year-round in temperate climates. Humans are the only known reservoir of infection, and the rubella virus is transmitted through direct inter-human contact through the aerosol route. After being inhaled, the virus replicates in the respiratory mucosa and cervical lymph nodes, before reaching the target organs via systemic circulation. The infectious period extends approximately 8 days before to 8 days after the rash onset. Viremia is transient and is detected during the week before the rash. Rubella is less contagious than measles or influenza; because many rubella cases are asymptomatic, the true attack rate is uncertain.

Rubella has a global distribution. The incidence of rubella varies according to age and the geographical zone. In industrialized countries, rubella epidemics have occurred every 5 to 9 years. Before the introduction of vaccination programs in 1968, infection predominantly affected the 5- to 9-year-old group, corresponding to the early school years.

The incidence of rubella has progressively decreased in many countries, and in industrialized countries, it is estimated to occur at a rate of 1.30/100 000 in the general population and 0.00/100 000 in the United States.[8] In the United States, rubella has been eliminated, although occasional imported cases are reported. Most sporadic cases occur in the immigrant population, originating in countries where rubella vaccination is not routine. In 1999, 81% of the reported cases occurred among persons of Hispanic descent, especially those from Mexico.[9,10] During 2004 to 2012, all 79 cases of rubella and six cases of CRS reported in the United States were imported or from unknown sources.[11] Since the implementation of rubella control strategies in the Americas,[12] the decline of rubella accelerated to the recent cessation of endemic transmission.[13] The European Region of the WHO has a goal to eliminate measles and rubella by the year 2015.[14] Despite great efforts in Europe to eliminate measles and rubella, cases and outbreaks continue. In 2012 (December–November), 28 536 cases of rubella were reported by 26 European Union and European Economic Area countries, and 99% of the cases were from Poland and Romania.[15] Most cases were not laboratory confirmed, and in 2009, only 492 of the 8827 reported cases (5.5%) were confirmed by laboratory analysis.[16]

In developing countries, the rate of susceptibility to rubella among women of childbearing age is low because of the scarcity of the rubella vaccine. However, as rubella viruses circulate in young children, the risk of primary infection for the rare susceptible women is higher. In recent years, a surveillance program for rubella and measles has been established, following the WHO African Regional Office guidelines for measles surveillance.[17,18] In the Western Pacific Region, rubella surveillance was integrated into the measles elimination system; some countries have not included rubella vaccination in their national immunization program. In 2011, in Vietnam, 65% of the cases occurred in women of childbearing age. In 2010, in the Lao Peoples Democratic Republic, 36% of 15- to 19-year-old women were not protected against rubella. However, the rubella vaccine was introduced in this country in November 2011, targeting individuals 9 months to 19 years old.[19]

VACCINATION

Since rubella vaccines were introduced in 1969, vaccination strategies have led to the elimination of rubella and CRS in many countries.

The most commonly used rubella vaccines are based on the live, attenuated RA 27/3 strain grown in human diploid cells; Japan and China use the TO-336 and BRD-2 strains, respectively. Rubella vaccines exist as monovalent preparations or are associated with vaccines against measles, measles and mumps or measles, mumps and varicella.

The antibody response rate to a single dose is higher than 95%. After two doses, the response rate approaches 100%, and immunity is detectable at over 21 years of age, despite waning rubella virus-specific immunoglobulin G (RV-IgG) titers.[20–23]

In most countries, the schedule for rubella vaccination is two doses before 24 months, which is identical to the schedule for measles vaccination.[24] In France, adults born after 1980 and seronegative children older than 24 months of age are administered two doses of trivalent vaccine.[25]

Rubella vaccines are generally well tolerated, and most of the adverse effects are benign. Fever (15%), rashes (5%), transient lymphadenopathy or parotiditis could be observed. Moderate to severe sequelae such as febrile seizures, anaphylaxis, thrombocytopenic purpura or encephalitis are very rare.[26] A significantly higher incidence of acute joint manifestations has been observed in postpubertal female subjects after vaccination, as have arthralgia and arthritis.[27]

Because of a theoretical teratogenic risk of the rubella vaccine, vaccination during pregnancy or becoming pregnant in the month following immunization is not recommended. A 1971 to 1988 study conducted by the Centers for Disease Control in women vaccinated during pregnancy or 3 months before conception did not report any defect resulting from rubella, although a few newborns were positive for rubella virus-specific immunoglobulin M (RV-IgM), suggesting a subclinical infection.[28] A prospective comparative study of 94 cases showed that there were no more malformations or infected infants in the vaccinated group than in the control group.[29] Since this study, several publications have reported the absence of CRS after vaccination during pregnancy.[30–33]

Prevention of congenital infection from rubella is the major goal of rubella vaccination. The time required to completely eliminate rubella and CRS will depend on the strategy used and could vary from less than 10 to 30 years. One approach could reduce CRS by vaccinating young girls or women of childbearing age. Another strategy, which is used in most developed countries, immunizes boys and girls early in childhood and adults susceptible to rubella, aiming to stop the circulation of the rubella virus. Several vaccination programs have been organized in different regions of the world. In 2010, 67% of the WHO member states included rubella vaccines in their national immunization programs in association with measles vaccines.[8] The new vaccination program, the Global Measles and Rubella Strategic Plan 2012–2020, aims to eliminate measles and rubella in at least five WHO regions by the end of 2020. To reach this goal, vaccination coverage must achieve at least 95% with two doses of measles or measles and mumps vaccines. Epidemiological surveillance of measles and rubella has been organized in collaboration with the WHO Global Measles and Rubella Laboratory Network. Laboratory confirmation (RV-IgM) and identification of viral genotypes are recommended to provide an effective response to outbreaks.[34]

SIGNS AND SYMPTOMS

More than 50% of cases are asymptomatic. In clinically apparent cases, after an incubation period of 13 to 20 days, a prodromal illness that includes fever, malaise and adenopathy, particularly in the postauricular lymph nodes, occurs with viremia. A maculopapular rash develops that typically lasts 1 to 3 days and is characterized by small pink papules (Figure 1). It is sometimes atypical, scarlatiniform or purpuric. Importantly, clinical diagnosis of rubella is unreliable because similar rashes

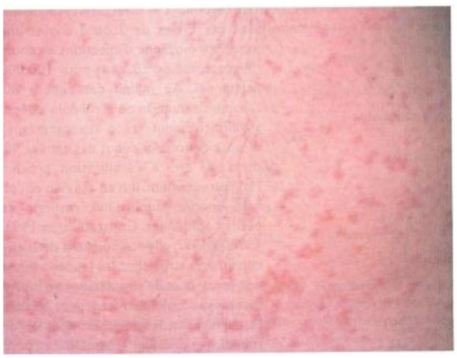

Figure 1 Rubella rash (Dr Wallach D. Cochin Hospital, Paris, France)

occur in other viral infections such as parvovirus B19, human herpes virus 6 and 7 and enteroviruses as well as in toxoplasmosis or allergic reactions.[35]

Polyarthritis and polyarthralgia are the most common complications, occurring generally in adult women and typically lasting 3 to 4 days; these symptoms occasionally persist for 1 month. Other manifestations, although rare, include post-infection encephalitis (approximately 1 in 6000 cases; recent epidemics report higher rates).[36] Thrombocytopenia, hemorrhagic manifestations and Guillain–Barré syndrome are rarely observed cases.[37]

RUBELLA RE-INFECTION

Rubella re-infection is a rubella infection in a person who already has rubella antibodies resulting from a documented natural rubella infection or successful rubella immunization.[38] Rubella re-infection is typically subclinical and frequently difficult to diagnose; however, a significant increase of antibody titers (IgG and/or IgM) can be observed. The incidence of re-infection during pregnancy is unknown, and the risk of transmission to the fetus is difficult to determine. Some prospective studies have shown that the risk of CRS is most likely less than 5%.[39] Among the viruses isolated from cases of rubella re-infection in pregnancy, one amino acid substitution has been found within the E1 region, suggesting that antigenic change is not responsible for rubella re-infection.[40,41]

DIAGNOSIS OF RUBELLA INFECTION

Rubella in the general population is a mild disease, and diagnostic tools have predominantly been developed for pregnant women, fetuses and newborns.

Natural immunity

The accurate diagnosis of rubella infection depends on an understanding of antibody kinetics. RV-IgM appear within 3 days after the rash and generally disappear in 4 to 12 weeks (the levels are divided by 2 every 3 weeks), primarily depending on the assay used. RV-IgG detected by ELISA appear slightly later (5–8 days after the onset of the rash) and persist throughout life. RV-IgG reach a steady state at any time from a few days to a few weeks, and the maximal and residual RV-IgG rates are extremely variable, depending on the patient tested and the assay used. A high RV-IgG titer is not necessarily a marker of a recent primary infection.

Determination of rubella immunity status

In developed countries, women of childbearing age are routinely screened for rubella antibodies to identify and vaccinate susceptible women.[39,42]

In France, the 2009 national recommendations stated, 'Given the current epidemiological situation, it is recommended that rubella serology is offered upon the first prenatal visit, unless there is written evidence of immunity or two doses of rubella vaccine documented'. If a patient is initially seronegative, another serology is performed at 20 weeks of gestation (WG); women who remain seronegative at 20 WG are offered vaccination after delivery.[43]

Immunity to rubella is normally determined by measuring the RV-IgG with enzyme immunoassays that provide quantitative results in international units (IU) per milliliter. The RV-IgG results and interpretation may be discordant, depending on the assay used, although the results are expressed in IU per milliliter and all the immunoassays are calibrated with the identical international standard (RUB-1-94). Preliminary studies indicate that the women are typically immune in cases in which discrepant results are observed. Specific assays such as immunoblots are used in these cases. Latex agglutination tests, which are qualitative or semi-quantitative assays, are no longer recommended.[39,44]

Diagnosis of maternal rubella infection

The clinical diagnosis of rubella is difficult and unreliable because of its inconsistent and non-specific clinical symptoms. Clinical diagnosis of Rubella is even less reliable in industrialized countries as it has become a rare disease.[45,46] Laboratory diagnosis is essential to confirm a recent rubella infection and is based on the observation of a seroconversion, on the kinetics of RV-IgG, RV-IgM and RV-IgG avidity and on the detection of rubella virus in nasopharyngeal secretions by reverse transcription/polymerase chain reaction (RT-PCR).[47,48]

In cases in which a pregnant woman has contact with a suspected rubella case, a serum sample should be tested for RV-IgG as soon as possible (<12 days) to determine her immune status. An RV-IgG-positive result could reassure the patient. If the patient is susceptible, a determination of RV-IgG and RV-IgM titers is recommended 3 weeks later to exclude an asymptomatic primary rubella infection (Figure 2). Physicians must be aware that following the primary infection, depending on the patient tested and on the assays used, RV-IgG could reach a steady state in a few days or a few weeks after the onset of the infection. Consequently, a woman seropositive at the first screening test may have been infected a few weeks earlier. Therefore, in case of ultrasound abnormalities (including intrauterine growth retardation), extra serological investigations should be performed on the earliest serum available (especially RV-IgM and RV-IgG avidity testing), and rubella RT-PCR in amniotic fluid (AF) should be discussed even in countries that tend to rubella elimination, and especially if the

Figure 2 Algorithm for the follow-up of women in contact with suspected rubella cases or exposed to rash during pregnancy

woman was born in a country that did not implement routine rubella vaccination in childhood.

In countries in which the rubella virus has almost disappeared, even in the context of a clinical presentation of the rash, seroconversion and positive RV-IgM assessments must be interpreted with caution, and further testing (RV-IgG avidity and/or immunoblot) in specialized laboratories should be performed. RV-IgM is almost always detected after the primary infection (if sampling is performed in the 2 months following the onset of infection) using the most sensitive technique; therefore, it could be detected in other situations. In countries in which vaccination is recommended, a positive RV-IgM result is typically from vaccination or non-specific stimulation of the immune system. Low concentrations of RV-IgM could be detected for months and even years after vaccination.[49] RV-IgM could reappear during a re-infection,[50] and false-positive reactivity has been reported.[51,52] In countries in which rubella is endemic, a positive RV-IgM has a good predictive value.

Rubella virus-specific immunoglobulin G avidity has been shown to benefit the dating of primary rubella infections. Different methods are used to measure the avidity index, and they are typically based on the use of a denaturing agent to prevent the binding of a low-avidity antibody to the antigen.[53–55] A low RV-IgG avidity index is frequently measured in recent primary infections (<1–3 months); a high RV-IgG avidity index excludes a recent primary infection (<3 months). RV-IgG avidity should be interpreted with caution in cases in which the RV-IgG titer is excessively low. After vaccination, the RV-IgG avidity index matures slowly and frequently stabilizes to a moderate value.[49]

CONGENITAL RUBELLA SYNDROME

In 2008, the number of infants born with CRS exceeded 110 000, with the highest rates in Southeast Asia (approximately 48%) and Africa (approximately 38%).[56] In France, the incidence of CRS was estimated at 1.01/100 000 live births in 2011.[57]

Pathogenesis

The rubella virus is responsible for chronic fetal non-lytic infections, and it might affect any organ. The pathogenesis of CRS is multifactorial.[58]

- Non-inflammatory necrosis in the epithelium of the chorion and in the endothelial cells is observed. These cells are transported to the fetal circulation and fetal organs such as eyes, heart, brain and ears, prompting thrombosis and ischemic lesions.
- Actin assembly is inhibited directly or indirectly in rubella infection, leading to the inhibition of cell mitosis and development of organ precursor cells.

- The immune system might play a role because interferon and cytokines appear to be upregulated in rubella-infected human fetal cells, which could disrupt developing and differentiating cells and thus contribute to congenital defects.[59]

In children with CRS, the rubella virus persists and is detected in urine, saliva and cerebrospinal fluid for several months,[47] which could be explained by a defect in cell-mediated immunity.[60] T-cell abnormalities have been observed in young adults with CRS, possibly leading to organ-specific autoimmunity disorders.[61]

Fetal infection incidence

The risks of congenital infection and defects depend on the gestational age at infection. Miller *et al.* showed that before 11 WG, the congenital infection rate approaches 90%, decreases to 30% between 24 and 26 WG and increases to nearly 100% beyond 36 WG. During the first 12 WG, the risk of major fetal defects nears 85%, with approximately 20% of the cases resulting in spontaneous abortions in the first 8 WG. The risk declines rapidly and fluctuates between 11 and 18 WG, approaching 0% after 18 WG (Table 1).[62]

The risk of fetal infection in cases in which conception occurs after the rash is most likely very low, and the rash is concomitant with the appearance of antibodies and the end of viremia. No intrauterine infection has been detected in the children or fetuses whose mothers had a rash before or within 11 days after the last menstrual period. Teratogenic infections could occur in pregnancies in which the rubella rash appears 3 to 6 weeks after the last menstrual period.[63]

Fetal manifestations

A viral rubella infection during embryogenesis leads to the classic triad of cataracts, cardiac abnormalities and sensorineural deafness, and many other defects might be observed. These abnormalities are classified as transient, permanent or late onset.[64] The transient defects in newborns include low birth weight, thrombocytopenic purpura, hemolytic anemia, hepatosplenomegaly and meningoencephalitis. Permanent defects include ophthalmic abnormalities (microphthalmia, cataracts and retinopathy), auditory impairment (sensorineural deafness), cardiac defects (patent ductus arteriosus and pulmonary artery hypoplasia),[65] central nervous system manifestations (mental or psychomotor retardation and language delay) and craniofacial malformations (microcephaly). Deafness is the most common defect and could be the only defect observed, particularly in cases in which infection occurs at 12 to 18 WG. Late-onset manifestations include endocrine, cardiovascular and neurological abnormalities. A review of 125 adults with congenital rubella (United States) reported ophthalmic damage as the most common disorder (78%), followed by sensorineural deafness (66%), psychomotor retardation (62%) and cardiac defects (58%), and 88% of the cases included other organ defects.[66] Additionally, CRS is associated with autoimmunity diseases, and several studies have reported an increased risk for diabetes and thyroid diseases.[67–70]

Table 1 **Cases of congenital infection and congenital defects after maternal rubella infection at different stages of pregnancy**

Gestational age (weeks)	Rate of congenital infection	No. with congenital defects/no. infected (%)
<11	9/10 (90%)	11/13 (85)
11–12	4/6 (67%)	
13–14	12/18 (67%)	9/26 (35)
15–16	17/36 (47%)	
17–22	33/92 (36%)	
23–26	8/32 (25%)	
27–30	11/31 (35%)	
31–36	15/25 (60%)	
>36	8/8 (100%)	

Source: adapted from Miller *et al.* (1982).[62]

Diagnosis of congenital rubella infection

Prenatal diagnosis

A prenatal diagnosis of congenital infection is recommended when a maternal infection is diagnosed and is based on the detection of RV-IgM in fetal blood or on the detection of the viral genome in AF, fetal blood or chorionic villus biopsies.[47,71] The detection of rubella virus in chorionic villus biopsies reflects an infection of the villi, not a fetal infection.

The specificity of a prenatal diagnosis is approximately 100%, and the sensitivity is greater than 90% if the following conditions are met: (i) at least a 6-week period passes between the infection and sampling; (ii) a sample collection is performed after 21 WG; and (iii) the samples for RT-PCR are stored and transported frozen (fetal blood for RV-IgM detection is stored and transported at 4 °C).[71]

Postnatal diagnosis of congenital infection

A postnatal diagnosis of congenital infection is based on the detection of a specific RV-IgM by immunocapture ELISA, which has sensitivity and specificity that approach 100% in infected newborns (<3 months of age[72]). In cases in which the RV-IgM test is positive, a congenital infection might be confirmed by isolating the rubella virus or by detecting the viral genome in nasopharyngeal swabs, urine and oral fluid using RT-PCR.[73]

Performing a postnatal diagnosis of a congenital infection is important, regardless of whether a clinical manifestation of CRS is observed, to provide a specific follow-up care plan if an infection is discovered (including neurological and hearing monitoring).[47]

A child infected *in utero* could excrete the virus in saliva and urine for several months or years.

MANAGEMENT OF RUBELLA INFECTION IN PREGNANT WOMEN

General management

The management of rubella infection depends on the gestational age at the onset of infection.

- **Infection before 18 WG**: The fetus is at high risk for infection and severe symptoms. Termination of pregnancy could be discussed and accepted, according to local legislation, particularly if the infection presented before

Figure 3 Fetal face at 19 WG (coronal view): microphthalmia and hyperechoic lens (arrow; Dr O. Picone)[45]

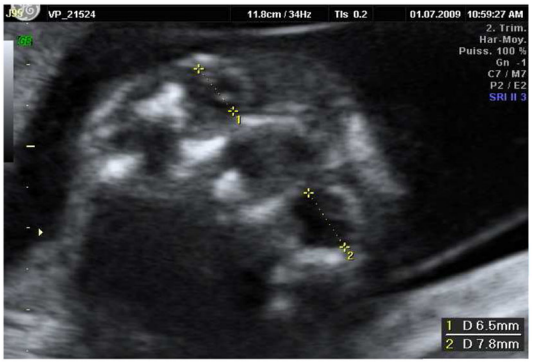

Figure 4 Fetal face at 19 SA (coronal view): ophthalmic asymmetry and microphthalmia (Dr O. Picone)[45]

12 WG. A detailed ultrasound examination and assessment of AF viral RNA are recommended, particularly for infections occurring between 12 and 18 WG. If a prenatal diagnosis is not performed, a specific pediatric examination must be performed in newborns, including RV-IgM assays.

- **Infection after 18 WG**: The pregnancy could be continued with simple ultrasound monitoring. A specific pediatric examination of the newborn and testing for RV-IgM are recommended.

Ultrasound findings

The most common ultrasound abnormalities are cardiac (septal defects) and ocular (cataracts and microphthalmia) defects (Figures 3 and 4).[45] Microcephaly, hepatomegaly, splenomegaly and intrauterine growth retardation are found less frequently.[74] No descriptive series of fetal ultrasound semiology has been reported that could determine the frequency of these abnormalities. Epidemics frequently occur in developing countries in which fetal ultrasound is not widely practiced. A preliminary study analyzed the role of ultrasonography (USG) in the prenatal diagnosis of congenital infection and defined the specificity of USG at 100% and the sensitivity at 11%; however, the series was small.[75]

CONCLUSION

There has been significant progress in preventing CRS since the discovery of the teratogenic potential of the rubella virus in 1941; however, further efforts are required to eliminate CRS.

Elucidating rubella virus pathogenicity is difficult because animal models to reproduce the human disease progression are lacking. The mechanisms for rubella-mediated teratogenesis and the interactions of the virus with the host immune system are not fully understood. Future studies should examine the long-term autoimmune effects of congenital rubella in humans.

The significance of IgM has been partially established in the diagnosis of maternal infection. The measurement of RV-IgG avidity is beneficial to the diagnosis of primary infection. Prenatal diagnoses of fetal infection performed by RT-PCR on AF are very reliable.

Although progress has occurred in the past 20 years, cases of rubella infection in pregnant women are detected every year, predominantly, however not entirely, in developing countries; increased rates of vaccination are necessary. The new strategic plan that aims to eliminate rubella and measles by the end of 2020 is generating new hope for the eradication of these diseases.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Congenital rubella is rare in developed countries, but potentially devastating fetal complications can occur.

WHAT DOES THIS STUDY ADD?

- Once rubella is suspected in a pregnant woman, management is based on biological diagnosis, which should be performed in specialized laboratories.
- There is a lack of data concerning the ultrasound semiology of congenital rubella.
- Vaccination against rubella must be improved, especially in developing countries.

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