

Rubella in pregnancy. Still a concern

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ABSTRACT

Rubella is the most important preventable cause of fetal malformations. Infection during pregnancy can result in fetal growth restriction, miscarriage, fetal death or it can cause congenital rubella syndrome with visual, auditory and cardiac defects. There are still many developing countries which are endemic for Rubella, despite major vaccination programmes available worldwide. There are no clinical symptoms present in approximately one half of cases, so diagnosis relies on serological testing if infection is suspected. Detection of IgM specific antibodies is the method of choice for diagnosis of both postnatal and congenital rubella. It has high sensitivity, but false positive cases are always possible after infection with other viruses like parvovirus B19, Epstein-Barr virus, cytomegalovirus and measles. Prevention relies on preconception care when it is recommended to check the immunity status for rubella (IgG) and for non-immunized patients, vaccination should be indicated.

Keywords: rubella, pregnancy, infection, congenital, prevention, vaccine

INTRODUCTION

Rubella, also known as German measles, is a mild febrile childhood disease with a characteristic rash, lymphadenopathy and transient polyarthralgia. It is primarily transmitted through direct or droplet contact from nasopharyngeal secretions. The leading concern involves pregnant women if the infection is acquired during pregnancy, particularly during the first trimester of pregnancy. Rubella is the main cause of fetal malformations, altogether known as congenital rubella syndrome (CRS), that could be prevented by vaccines. Since the early 1970s, vaccination has been available, reducing the incidence of infection in countries that have well-developed immunization programs.

METHODS

A systematic electronic search was undertaken for primary articles, reviews and guidelines using

PubMed. Also, recommendations from CDC (Centers for Disease and Prevention), WHO (World Health Organization) were included. Search words were “rubella” and “pregnancy”. All the publications used can be found in the reference section.

EPIDEMIOLOGY

Before the introduction of the rubella vaccine, rubella was endemic worldwide with epidemics occurring every 6-9 years and major pandemics occurring every 10 to 30 years [1]. In Europe, incidence declined by >99%, from 234.9 cases per 1 million population (206,359 cases) in 2005 to 0.67 cases per 1 million population (620 cases) by 2019, after the Regional Committee of the World Health Organization (WHO) European Region (EUR) addressed a claim calling for the local elimination of measles, rubella, and congenital rubella syndrome (CRS) in 2005 [2]. In 2015, the Pan American Health Organization of the World Health Organization an-

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nounced that the North, Central and South America is the world's first region to eliminate rubella and congenital rubella syndrome [3]. This evidence clearly demonstrates the effectiveness of rubella vaccines. Nowadays, rubella cases in developed countries are mainly brought from those countries where rubella is still endemic and occur mostly in inadequately vaccinated or unvaccinated individuals [1].

As of the end of 2018, 168 of 194 countries (87%) included 2 rubella-containing vaccines doses as part of a combination vaccine with measles and mumps (MMR) - or measles, mumps, and varicella (MMRV) vaccine in their routine childhood vaccination schedule with 81 (42%) countries eliminating transmission of rubella [4].

Despite this progress, intermittent outbreaks of rubella may still occur in countries that have a good national immunization program if there is a substantial proportion of the population that remains susceptible. For example, in Japan the vaccination program included only adolescent women since 1976 and all children aged one to six years since 1989. The incidence of rubella cases remained low from 2000-2010 with a rapidly increase in 2013 and again in 2018, most of these cases attributed to susceptible men aged 20-49 years who were not included in the initial rubella immunization schedule [5].

The highest incidence rates of rubella worldwide are reported in African and Southeastern Asian countries [6]. For Europe, the highest incidences in 2019 were in Poland and Ukraine. The last documented outbreaks were reported in Romania in 2012 (1,873 cases) and Poland in 2013 (38,548 cases) [7].

CLINICAL MANIFESTATIONS

Postnatally acquired rubella is characterized by mild fever with a maculopapular rash that usually starts on the face and becomes generalized within 24 hours, along with lymphadenopathy that precedes the rash, often involving posterior auricular or suboccipital lymph nodes. The rash lasts on average 3 days and the lymphadenopathy lasts between 5 to 8 days. No symptoms are described in 25-50% of cases. Giving that up to half of all infections may be subclinical, clinical diagnosis is unreliable. Also, the rash is not pathognomonic and it can be easily mistaken with other childhood illnesses [8].

The average incubation period for rubella virus is 17 days, ranging between 12 to 23 days. Viremia is high when the rash is erupting and people can be contagious up to one week before that and up to 1 week after the rash appears [8].

Congenital rubella infection may lead to fetal death *in utero*, preterm delivery, or congenital de-

fects, known together as congenital rubella syndrome, if the infection occurs in the first trimester. During the second trimester, the risk for congenital defects is really low and for the third-trimester, the only possible complication is fetal growth restriction [9]. Deafness, cataracts, and cardiac disease are the classic manifestations of congenital rubella syndrome, but there can be many more manifestation mentioned in the table below.

TABLE 1. Clinical manifestations of CRS – adapted from [10]

	Type	Frequency
Early manifestation	Hearing impairment	60%
	Congenital heart disease	45%
	CNS abnormalities	27%
	Congenital cataract	25%
	Fetal growth restriction	23%
	Hepatosplenomegaly	19%
Late manifestation	Hearing loss	80%
	Diabetes mellitus	10-15%
	Intellectual disability	13%
	Thyroid dysfunction	5%

CNS – central nervous system, CRS – congenital rubella syndrome

In cases of suspected/confirmed CRS, antenatal ultrasound screening should be performed in order to describe the possible fetal anomalies. The number of cases in developed countries declined significantly in the last 2 decades, and given the fact that these are also the places with good antenatal screening programs, there is not much data available about the sonographic aspects of CRS. According to a review published in 2017, the most frequent prenatal sonographic findings when the infection occurs before 20 weeks of gestation, were IUGR, cerebral malformations (e.g., microcephaly), ocular defects (e.g., cataract, microphthalmia) and cardiac defects (e.g., pulmonary artery stenosis) [11].

DIAGNOSIS

As mentioned before, the clinical manifestations of rubella infection are non-specific and in 25-50% of the cases, the patient is asymptomatic. Therefore, only in case of recent exposure to a confirmed case or travel to an endemic area, with/without matching symptoms, further diagnostic work-up should be engaged. In case of suspected infection, detection of IgM specific antibodies is the method of choice for diagnosis of both postnatal and congenital rubella. It has high sensitivity, but the specificity is not absolute and false positive cases are always possible.

False positive cases can occur after infection with other viruses like parvovirus B19, Epstein-Barr

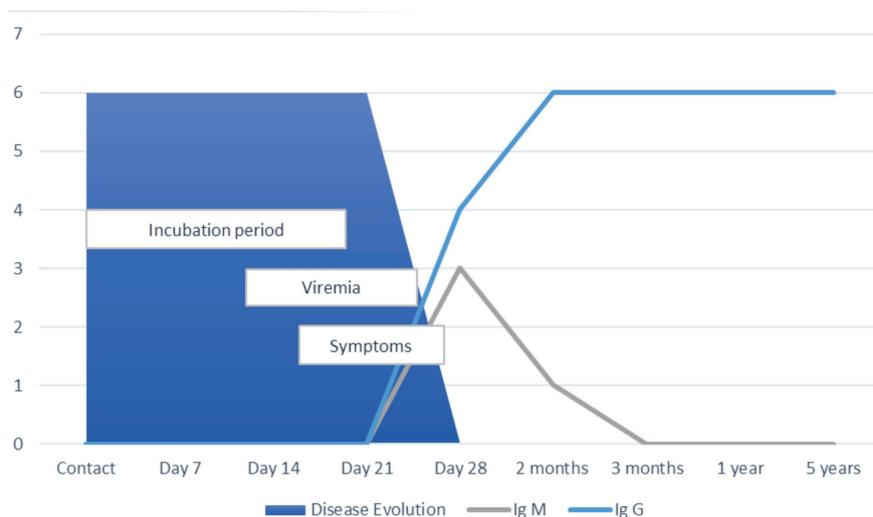


FIGURE 1. Disease evolution: Clinical and serological findings (personal drawing, Ana Scutelnicu)

virus, cytomegalovirus and measles. Also, the rheumatoid factor can interfere with rubella IgM and it can be found in 10% of the asymptomatic population or in cases of other bacterial or viral infections [12].

Therefore, after a positive IgM test, further investigations are required to confirm or exclude the acute infection. Although rubella virus can be isolated from nasopharyngeal, throat and urine samples in the first 7 days after the rash appears, viral culture or RT-PCR techniques are expensive, time consuming and not easily available, so they are not recommended. A fourfold increase in IgG titers can be used to reliably confirm recent infection with two samples required –one within 7 days post-rash and another at least 20 days after rash onset. If no rash or other symptom is present when timing of infection is unknown and in the presence of positive IgM, it is recommended to measure IgG avidity. A low avidity rubella IgG combined with a positive IgM strongly suggests infection in the past 2 months. Contrarily, a high avidity index indicates a more remote infection [13].

PREVENTION – PRECONCEPTION/PRENATAL AND POST-PARTUM

Rubella is the most important vaccine-preventable cause of birth defects. Infection during pregnancy can result in fetal growth restriction, miscarriage, fetal death or it can cause CRS with visual, auditory and cardiac defects. Although there are parts of the world such as the Americas and many developed European countries that have eradicated this disease, there are still some endemic areas where rubella is a major public health issue.

The main purpose of rubella vaccination is to prevent CRS and it's efficacy is clearly demonstrat-

ed since 1969, when the first vaccine was licensed for general use. Preconception care is key in documenting immunity and vaccinating individuals who are not immunized, with the clear recommendation to avoid getting pregnant for 28 days following vaccination. In most regions with low prevalence, combination measles, mumps and rubella (MMR) vaccine is used for routine childhood vaccination as well as vaccinating the susceptible non-pregnant adolescents and adults, but mainly persons born in countries with unreliable immunization program.

Documenting rubella immunity is a standard recommendation of prenatal care. Once immunity to rubella is proved as a result of either infection or immunization, repeat testing is unnecessary. If the patient has no immunity against rubella, the standard recommendation should be to avoid exposure and receive postpartum immunization. The rubella vaccine is a live attenuated vaccine and thus contraindicated during pregnancy.

MANAGEMENT AND RECOMMENDATIONS

Rubella infection rates vary greatly around the globe so management is different in endemic areas versus areas with low/zero incidence. For example, Centers for Disease Control and Prevention (CDC) in the United States discourages the use of rubella IgM for rubella screening in pregnancy [14]. This is recommended mainly because of issues of false-positivity and the low incidence of the disease. Nevertheless, immunity status for rubella (IgG) should be checked during preconception or, if not possible, during the first prenatal visit. Although there are no clear recommendations made by national/international guidelines for rubella screening in endemic

areas, it could be useful to check for both IgG and IgM in the first trimester.

Postpartum vaccination is recommended in seronegative women giving that the vaccine is live attenuated and it's contraindicated during pregnancy. Breastfeeding is not contraindicated following vaccination.

CONCLUSIONS

Since the discovery of the teratogenic potential of rubella infection, there has been significant progress in preventing CRS. However, there is still a long way to go to completely eliminate the disease around the globe. This is mainly a childhood disease, but considering the non-immunized women, it

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represents an important global health care issue. The clinical manifestations of rubella infection are non-specific and in many cases the patient is asymptomatic. Therefore, diagnosis is difficult if not clinically suspected. IgM detection is the method of choice for diagnosis with possible addition of IgG avidity in case of unclarity. Documenting rubella immunity is a standard recommendation of preconceptional care and vaccination should be offered in case of negative result.

Although progress has been made in the past 20 years, cases of rubella infection in pregnant women are detected every year, predominantly, in developing countries. The aim for the future should be focusing on increasing vaccination rates in areas like Africa, Southeast Asia and Eastern Europe.