

Rubella in Pregnancy

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Abstract

Objective: To provide an update on rubella and pregnancy so that health professionals remain aware of the potentially devastating effects on the developing fetus.

Outcomes: Rubella vaccination has been effective in virtually eliminating congenital rubella syndrome in Canada.

Evidence: Medline, PubMed, and Cochrane Database were searched for articles published between 1985 and 2007.

Values: The quality of evidence was rated using the criteria described in the report of the Canadian Task Force on Preventive Health Care.

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Key Words: Rubella, congenital rubella syndrome, pregnancy, immunization

Recommendations

1. Since the effects of congenital rubella syndrome vary with the gestational age at the time of infection, accurate gestational dating should be established, as it is critical to counselling. (II-3A)
2. The diagnosis of primary maternal infection should be made by serological testing. (II-2A)
3. In a pregnant woman who is exposed to rubella or who develops signs or symptoms of rubella, serological testing should be performed to determine immune status and risk of congenital rubella syndrome (III-A)
4. Rubella immunization should not be administered in pregnancy but may be safely given post partum. (III-B)
5. Women who have been inadvertently vaccinated in early pregnancy or who become pregnant immediately following vaccination can be reassured that there have been no cases of congenital rubella syndrome documented in these situations. (III-B)
6. Women wishing to conceive should be counselled and encouraged to have their antibody status determined and undergo rubella vaccination if needed. (I-A)

INTRODUCTION

Rubella, also called German measles, is a disease of childhood that has markedly declined in incidence in North America since the introduction of routine childhood rubella vaccination. In the absence of pregnancy, it is usually clinically manifested as a mild self-limited infection.¹ During pregnancy, however, the virus can have potentially devastating effects on the developing fetus. It has been directly responsible for inestimable wastage and for severe congenital malformations.¹ This document will review some of the implications of rubella during pregnancy. Recommendations are evaluated using the evidence criteria of the Canadian Task Force on Preventive Health Care (Table 1).²

EPIDEMIOLOGY

The rubella vaccination program introduced in 1969 has been very effective.³ Rubella and the CRS have largely been eliminated in Canada.⁴ However, cases of CRS continue to occur in Canada and other parts of the world, thus CRS remains a concern.⁵

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.²

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.²

In Canada, before the introduction of rubella vaccine in 1969, rubella epidemics occurred at irregular three- to ten-year intervals. After 1970, the incidence of rubella declined markedly and has stayed at a mean endemic rate of 4/100 000 population per year. This is an average of 1000 cases reported/year, range 237 to 2450.⁵ Rubella virus continues to circulate in the community, and not all pregnant women are immune. Some segments of the population are not immunized against rubella because they are missed, refuse immunization, or come from countries where rubella vaccination is not part of the routine immunization program.⁵

Large rubella outbreaks occurred in Canada in the 1990s. The outbreaks were a reflection of Canadian immigration policies in the 1970s and 1980s, and current international immunization policies.⁵ In 2005, 220 cases of rubella were

confirmed in three counties in Ontario. The majority of these cases were in members of a religious community in which many members had not been vaccinated or had not accepted the full range of vaccines routinely recommended.⁶ This is a reminder that rubella is not only a disease of unimmunized immigrants. Epidemics do occur in Canada, and pregnant women born in Canada may be at risk of infection.

CLINICAL MANIFESTATIONS

In a non-pregnant woman, rubella is usually an infection of minor impact characterized by a mild, self-limited disease associated with a characteristic rash.^{1,6} The incubation period for rubella is 12 to 23 days. The infectious period is from 7 days before to 5–7 days after rash onset.¹ Although rubella is asymptomatic in 25% to 50% of cases, some individuals may experience mild prodromal symptoms such as low-grade fever, conjunctivitis, sore throat, coryza, headaches or malaise, and tender lymphadenopathy. These prodromal symptoms will usually last one to five days before the onset of the scarletiform rash, which may be mildly pruritic.⁴ The rash characteristically begins on the face and spreads to the trunk and extremities. It will usually resolve within three days in the same order in which it appeared (face first and then body).⁷

Polyarthritides and polyarthralgias are potential sequelae, developing mostly in adolescent and adult women (60–70%) about one week after the rash.⁸ Classically, the hands, knees, wrists, and ankles are affected symmetrically,

ABBREVIATIONS

CI	confidence interval
CRS	congenital rubella syndrome
CVS	chorionic villus sampling
ELISA	enzyme linked immunoassay
FGR	fetal growth restriction
IgG	immunoglobulin G
IgM	immunoglobulin M
MMR	measles, mumps, rubella
PCR	polymerase chain reaction

Table 2. Congenital defects and late manifestations of rubella infection

Present at birth	Late manifestations
Audiologic anomalies (60–75%)	Diabetes mellitus
Sensorineural deafness	Thyroiditis
Cardiac defects (10–20%)	Growth hormone deficit
Pulmonary stenosis	Behavioural disorder
Patent ductus arteriosus	
Ventricular septal defect	
Ophthalmic defects (10–25%)	
Retinopathy	
Cataracts	
Microphthalmia	
Pigmentary and congenital glaucoma	
Central nervous system (10–25%)	
Mental retardation	
Microcephaly	
Meningoencephalitis	
Others	
Thrombocytopenia	
Hepatosplenomegaly	
Radiolucent bone disease	
Characteristic purpura (Blueberry muffin appearance)	

and the pain will last about one to four weeks. Chronic arthritis rarely develops. Other manifestations, although rare, include tenosynovitis, carpal tunnel syndrome, thrombocytopenia, post-infectious encephalitis, myocarditis, hepatitis, hemolytic anemia, and hemolytic uremic syndrome.^{9,10}

CONGENITAL RUBELLA SYNDROME

CRS represents the neonatal manifestations of antenatal infection with the rubella virus. The infection affects many fetal systems.^{1,11,12} The risk of CRS abnormalities varies according to the gestational age at which the maternal infection occurs.⁷ Therefore, counselling regarding the risk to the fetus and management of pregnant women must be individualized. Transplacental vertical infection by the rubella virus can have catastrophic effects on the developing fetus, resulting in spontaneous abortion, fetal infection, stillbirth, or fetal growth restriction.¹³ Many children born with CRS will demonstrate persistent neuromotor deficits later in life. Pneumonitis, diabetes mellitus, thyroid dysfunctions, and progressive panencephalitis are other late expressions of CRS.^{14,15}

The most common congenital defects and late manifestations are shown in Table 2.^{12,14,15}

VERTICAL TRANSMISSION AND RISK OF CRS

Fetal infection is acquired hematogenously, and the rate of transmission varies with the gestational age at which maternal infection occurs. After infecting the placenta, the rubella virus spreads through the vascular system of the developing fetus, causing cytopathic damage to blood vessels and ischemia in developing organs.¹⁶

When maternal infection/exposure occurs in the first trimester, fetal infection rates are near 80%, dropping to 25% in the late second trimester and increasing again in the third trimester from 35% at 27–30 weeks’ gestation to nearly 100% beyond 36 weeks’ gestation.⁷ The risk of congenital defects has been reported to be 90% when maternal infection occurs before 11 weeks of gestation, 33% at 11–12 weeks, 11% at 13–14 weeks, 24% at 15–16 weeks, and 0% after 16 weeks.⁷

Therefore, the risk of congenital defects after maternal infection is essentially limited to the first 16 weeks of gestation. Little, if any, risk of CRS is associated with infection beyond 20 weeks, and FGR seems to be the only sequela of third trimester infection.^{7–17} Periconceptual maternal infection does not seem to increase the risk of CRS.¹⁸

Maternal immunity, either after vaccination or naturally derived, is generally protective against intrauterine rubella

infection.^{19,20} However, there have been cases of CRS after maternal reinfection.²⁰ Therefore, CRS should always be considered in a fetus or neonate with a clinical picture suggestive of congenital infection.¹⁹ It should be noted that no case of CRS has been reported when maternal reinfection occurred after 12 weeks of pregnancy.²¹

Recommendation

1. Since the effects of congenital rubella syndrome vary with the gestational age at the time of infection, accurate gestational dating should be established, as it is critical to counselling. (II-3A)

DIAGNOSIS OF RUBELLA INFECTION

Diagnosis of Maternal Infection

Accurate diagnosis of acute primary rubella infection in pregnancy is imperative and requires serologic testing, since an important number of cases are subclinical. Serology by ELISA to measure rubella-specific IgG and IgM is convenient, sensitive, and accurate. The presence of a rubella infection is diagnosed by:

- A fourfold rise in rubella IgG antibody titre between acute and convalescent serum specimens
- A positive serologic test for rubella-specific IgM antibody
- A positive rubella culture (isolation of rubella virus in a clinical specimen from the patient).¹

Serologic studies are best performed within 7 to 10 days after the onset of the rash and should be repeated two to three weeks later. Viral cultures drawn from nasal, blood, throat, urine, or cerebrospinal fluid maybe positive from one week before to two weeks after the onset of the rash.^{1,22}

Recommendation

2. The diagnosis of primary maternal infection should be made by serological testing. (II-2A)

Diagnosis of Fetal Infection

There are small series reporting the usefulness of rubella-specific PCR on CVS for the prenatal diagnosis of intrauterine rubella infection.^{23,24} This technique has proved to be superior to assessment of amniotic fluid samples in one study.²⁵ Because CVS is done at 10 to 12 weeks of gestation, it allows earlier detection than is possible with other samples, such as amniotic fluid taken at 14 to 16 weeks or fetal blood obtained at 18 to 20 weeks of pregnancy.

Ultrasound diagnosis of CRS is extremely difficult. Biometric data can aid in the diagnosis of FGR but are not a good tool for diagnosing CRS, given the nature of the malformations encountered. Any fetus presenting with FGR should be evaluated for congenital viral infections, including rubella.⁹

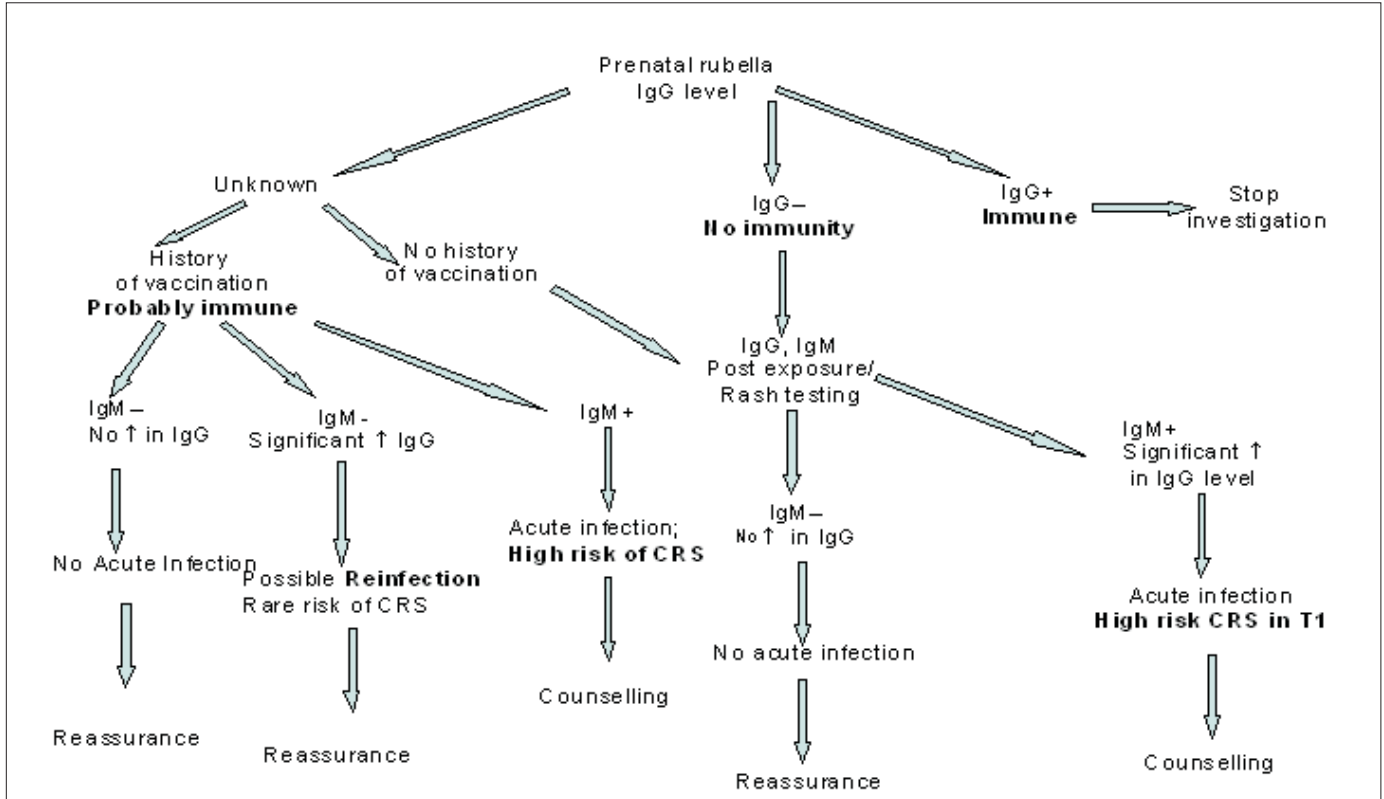
MANAGEMENT OF RUBELLA EXPOSURE/ INFECTION IN PREGNANT WOMEN

The management of the exposed pregnant woman must be individualized and depends when during gestation she was exposed and on her state of immunity. Confirmation of acute rubella infection in pregnant women is often difficult. Clinical diagnosis is unreliable because a large proportion of cases are subclinical and because clinical features can be very similar to those of other illnesses. The Figure shows a guide for the management of the exposed pregnant woman or woman presenting with rubella-like symptoms in pregnancy.

If a pregnant woman develops signs or symptoms of a rubella-like illness or has recently been exposed to rubella, gestational age should be determined as well as her state of immunity.

1. Known immune \geq 12 weeks of gestation.
 - a. No further testing is necessary. CRS has not been reported after maternal reinfection beyond 12 weeks' gestation.¹⁹
2. Known immune \leq 12 weeks of gestation.
 - a. If these women demonstrate a significant rise in rubella IgG antibody titre without detection of IgM antibody, they should be informed that reinfection is likely to have occurred.²⁰ Fetal risk for congenital infection after maternal reinfection during the first trimester has been estimated at 8% (95% CI 2–22%).¹⁹ Appropriate counselling should be provided.
3. Non-immune or immunity unknown.
 - a. Gestational age \leq 16 weeks.
 - i. Acute and convalescent IgG and IgM should be obtained. (The diagnosis of recent rubella infection should include serologic testing of acute sera for both IgG and IgM antibody.) Acute infection is diagnosed when IgM antibodies are positive. When IgM antibodies are negative or unavailable, testing of paired acute and convalescent sera for IgG antibody should be performed. During a rubella-like illness, the acute specimen should be drawn as soon as possible, followed by a convalescent specimen two to three weeks later if the first IgM specimen was negative. When there is a suspected exposure, the acute specimen should be drawn immediately, followed by a convalescent specimen 4 to 5 weeks later.

Management of exposed pregnant women



Adapted from ACOG Education and Technical Bulletins 2002

- b. Gestational age between 16 and 20 weeks.
 - i. Instances of CRS between 16 and 20 weeks' gestation are rare (< 1%) and may be manifested by sensorineural deafness (often severe) in the newborn. Appropriate counselling to the non-immune pregnant woman should be provided.
- c. Gestational age > 20 weeks.
 - i. A pregnant woman exposed to rubella or presenting with rubella-like illness after 20 weeks of gestation should be reassured, since no studies have documented CRS after 20 weeks.^{9,13,14,18}
- d. Diagnostic difficulty—late presentation with unknown immune status.
 - i. A pregnant woman presenting 5 weeks or more after exposure to a rash illness or 4 weeks or more after onset of a rash presents a diagnostic dilemma. If IgG antibodies are negative, the patient is clearly susceptible to rubella and has no evidence of a recent infection. If IgG are positive, there is evidence of a previous infection. It is then difficult to determine the date of infection and the

risk to the fetus, although a low level of antibody suggests more remote infection. Testing for IgM antibody or repeating the test for IgG antibody levels to determine whether there is a significant rise or decline may be considered.

Recommendation

- 3. In a pregnant woman who is exposed to rubella or who develops signs or symptoms of rubella, serological testing should be performed to determine immune status and risk of congenital rubella syndrome. (III-A)

TREATMENT

The treatment of acute rubella infection is supportive. The prognosis is generally excellent for pregnant women with rubella infection.

There are no data supporting the use of immunoglobulin in pregnant women with acute infection in order to diminish the fetal response to disease. The Centers for Disease Control recommend limiting its use to women with known rubella exposure who decline pregnancy termination.²⁶

THE VACCINE

The first live attenuated rubella vaccine was introduced in 1969. A single dose of this vaccine will result in measurable antibody in almost 95% of susceptible persons. Antibody levels persist for at least 18 years in more than 90% of the vaccine recipients.⁵ Primary failure of the rubella vaccine occurs in less than 5% of immunizations.²⁷ Although reinfection may occur in immunized pregnant women, these reinfections have resulted in only 8% risk of CRS in the first trimester of pregnancy.¹⁹

The rubella vaccine is usually well tolerated. Side effects to vaccination, although rare, include arthritis, arthralgia, rash, adenopathy, and fever.²⁷ The actual vaccine-related frequency of acute arthritis or arthralgia in non-immune women is in the order of 5% each. However, there is no evidence of any increased risk of new onset chronic arthropathies or neurological conditions in women receiving the RA27/3 rubella vaccine. There are no epidemiologic data supporting an association of CRS or autism to the MMR vaccine.²⁸

Contraindications to rubella vaccinations include febrile illness, immunodeficiency, history of an anaphylactic reaction to neomycin, and pregnancy.¹ Rubella vaccine virus has the potential to cross the placenta and infect the fetus.¹ However, **there has been no report of CRS in the offspring of women inadvertently vaccinated during early pregnancy.**^{29,30} Therefore, pregnancy termination is not recommended for these patients.³¹ Given the potential risks to the fetus, women are advised not to become pregnant for a period of 28 days after immunization.³²

The vaccine can be given safely to postpartum women who are breastfeeding and to the children of pregnant women, since infection is not transmitted from recently immunized individuals. Breastfeeding is NOT contraindicated.⁵ The vaccine can be administered in conjunction with other immune globulin preparations such as Rh-immune globulin.⁷

Recommendations

4. Rubella immunization should not be administered in pregnancy but may be safely given post partum. (III-B)
5. Women who have been inadvertently vaccinated in early pregnancy or who become pregnant immediately following vaccination can be reassured that there have been no cases of congenital rubella syndrome documented in these situations. (III-B)

PREVENTION

The best therapy for CRS is prevention. All girls should be vaccinated against rubella before entering the child-bearing years.

To prevent CRS, the following steps are recommended.

1. Providing universal infant immunization to decrease circulation of virus (instituted in all provinces in 1983).
2. Using measles, mumps, and rubella or measles-rubella vaccine as the immunizing agent in catch-up campaigns and as the second dose in the new two-dose routine immunization program for measles. (This may expedite the elimination of rubella).
3. Ensuring that girls are immune before they reach child-bearing age and using every opportunity to assess the immunity of women of child-bearing age and providing vaccination if necessary (pre-conceptual and infertility consultations).
4. Screening to determine the antibody status of all pregnant women to determine susceptibility.
5. Providing programs to ensure postpartum immunization of non-immune women before they are discharged from the hospital.
6. Screening for immunity and vaccination, if necessary, of all health care personnel, including students in training.
7. Immunizing all immigrant and refugee women at their first encounter with the Canadian health care system, unless they have documentation of effective vaccination or natural immunity.

Recommendation

6. Women wishing to conceive should be counselled and encouraged to have their antibody status determined and undergo rubella vaccination if needed. (I-A)

CONCLUSION

Rubella infection of a pregnant woman may have devastating effects on the developing fetus. The mainstay of prevention is the universal immunization of all Canadian infants and identification and immunization of immigrant women at risk. The diagnosis of infection should be made as soon as possible. Contact with rubella should be avoided throughout the first two trimesters of pregnancy, even in IgG-positive pregnant women. Women should be counselled about the possible risk of vertical transmission and offered pregnancy termination, especially if primary infection occurs prior to 16 weeks' gestation. Unfortunately, there is no in utero treatment available for infected fetuses. Thus, prevention remains the best strategy to eliminate all cases of CRS.

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