Congenital Diseases Learning Guide

CMV

Toxoplasma

Rubella

Abbott GmbH & Co. KG
Abbott Diagnostics Europe
Max-Planck-Ring 2
65205 Wiesbaden
Tel. (+49) 61 22 58 0
Fax (+49) 61 22 58 12 44
www.abbottdiagnostics.com

AB2201/uk Congenital Diseases Learning Guide 01/07/1

Abbott Diagnostics

Abbott
A Promise for Life

About this Learning Guide

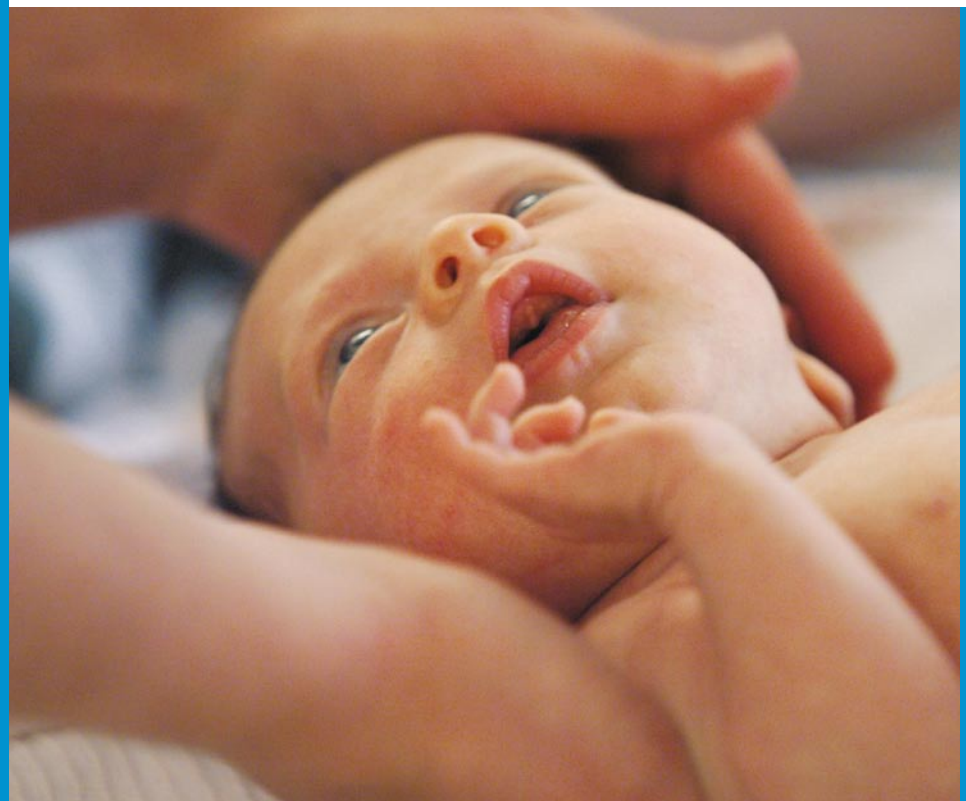
This publication covers current topics in the diagnosis, treatment, and prevention of Human Cytomegalovirus (CMV), *Toxoplasma (T. gondii)*, and Rubella virus infections.

Aimed at healthcare professionals, the purpose of this guide is to raise the awareness of how these diseases occur and how they can be prevented.

In addition to biology, pathology, epidemiology, diagnosis, treatment, and prevention, this guide provides real-world examples of patients affected by these diseases and the importance of proper diagnosis in clinical practice.

As you progress through the subsections, please review the learning objectives and complete the quizzes. There are a total of 6 quizzes, 2 per disease state.

Table of Contents



Human Cytomegalovirus

Contents

Introduction

Human Cytomegalovirus (CMV) is an ubiquitous herpesvirus in humans and is the leading cause of congenital virus infection in the US and Europe. Of the 4 million births in the US alone, approximately 40,000 (1%) are infected by CMV annually. Severe fetal damage occurs in approximately 2,000 to 3,000 of these births.

Intrauterine transmission of primary CMV infection, especially during the first trimester, has the most potential to cause significant fetal damage. Primary intrauterine CMV infections are second only to Down's Syndrome as a known cause of mental retardation. Congenital CMV infection is also a leading cause of sensorineural hearing loss and an important cause of cerebral palsy.

Since CMV infections are asymptomatic or accompanied by symptoms not specific to CMV, most maternal and congenital CMV infections are clinically silent and go undetected.

The general public is not well informed regarding this public health problem, and many physicians are uncertain as to the best approach to diagnose maternal and congenital CMV infection.

The control and diagnosis of maternal and congenital CMV infection requires that women considering pregnancy, pregnant women, daycare providers, physicians, laboratorians, and other health care providers be aware of:

1. Preventative measures to avoid CMV infection during pregnancy.
2. Diagnostic tests and algorithms for maternal and congenital CMV infection.
3. Prognosis or risk of sequelae or impairments.
4. Appropriate patient follow-up and treatment of symptomatic and asymptomatic congenital CMV infection.

This guide contains a review of the key features and diagnosis of maternal and congenital CMV infection, followed by a review of prevention and treatment measures.

Section 1:

The Biology & Pathology of CMV

In this section

Learning Objectives

After completing this section, you should be able to:

Indicate the physical features of the virus.

Indicate how CMV is transmitted.

Recognize the difference between primary and non-primary CMV infection.

Identify individuals at risk for CMV infection.

Understand the incidence and prevalence of CMV infections.

Describe symptoms associated with CMV infection.

Know the use of different tests used to detect CMV infection.

What is CMV?

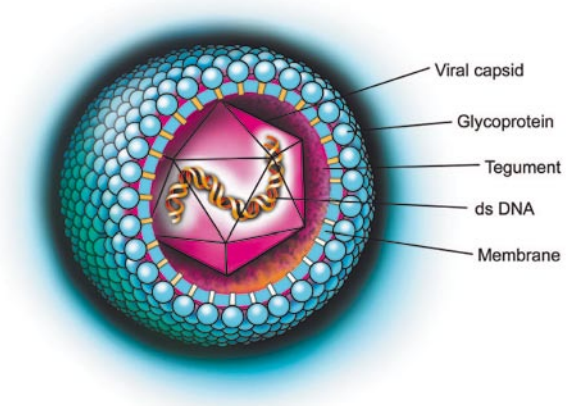
CMV is a DNA virus and a member of the herpes family of viruses. CMV establishes itself in the host in a latent form, and periodic nonprimary infections occur throughout the life of the infected person.

CMV is an enveloped virus: Between the envelope and the icosahedral-shaped capsid is an amorphous protein-filled region called tegument.

The genome consists of linear double stranded DNA.

Viral replication and assembly occurs in the nucleus.

Replicative cycles are long for CMV (72–94 hours).



Human Cytomegalovirus

Biology & Pathology

CMV is capable of infecting and damaging many different cell types, such as salivary glands, kidney, pancreas, adrenals, lung, liver, eye, ear, placenta, gastrointestinal tract, heart, ovaries, skin, blood vessels and various components of the central nervous system such as the brain, its coverings, and their blood vessels. Impaired organ function results from a combination of "lytic" (bursting) infection of cells and vascular compromise due to infection of vascular endothelial cells. The ability of CMV to infect white blood cells and vascular endothelial cells facilitates dissemination of virus within the host.

Primary Infection

Primary CMV infection occurs when the CMV virus infects a previously uninfected, seronegative individual. This can be demonstrated by seroconversion; i.e. the production of CMV IgM and IgG antibodies in a seronegative individual.

In the absence of documented seroconversion, the presence of CMV IgM antibodies and low avidity CMV IgG antibodies are indicative of a primary CMV infection.

Latency

Following primary CMV infection, CMV establishes latency in the host.

An important part of latency is the fact that the virus persists indefinitely and can be reactivated (to produce infection) by immunosuppression or other stimuli.

A small proportion of circulating monocytes in seropositive persons harbor latent CMV; when these monocytes are activated and differentiate into tissue macrophages, CMV is reactivated from latent to productive infection with release of infectious virus into surrounding tissue.

Nonprimary Infection

Nonprimary CMV infection occurs when a previously infected, seropositive individual experiences reactivation of a previous CMV infection from latency, or reinfection with a new strain of CMV.

Nonprimary CMV infection is usually characterized by the presence of high avidity CMV IgG antibodies.

Routes of Transmission

CMV is spread from person to person by close contact with body fluids that contain the virus. Young children play an important role in spreading CMV because their routine care can lead to contact with body fluids. In addition, CMV can be transmitted by blood transfusion and organ transplantation. Situations in which transmission of CMV often occurs include the following:

Daycare

Preschool-aged children in close daily contact often spread CMV to each other thus increasing the number of infected children and exposed parents in the community.

Child Rearing

Infants and young children with CMV infection shed virus in urine and saliva for many months, even years. They often transmit CMV to their susceptible caregivers, including their mothers, fathers, and child care workers.

Intrauterine Transmission

CMV can be transmitted from mother to fetus, resulting in congenital infection. If primary maternal infection occurs during pregnancy, there is about 1 chance in 3 that the fetus will be infected.

Intimate Contact

CMV is present in saliva and genital secretions of men and women and can be transmitted during sexual activity or intimate contact.

Breastfeeding

CMV is commonly spread from mother to child through breastfeeding. This can only occur if the mother has been infected by CMV. With rare exceptions, infants who acquire CMV by breastfeeding do not have signs or symptoms.

During Birth

If CMV is present in the birth canal, it can be transmitted from mother to baby (intrapartum transmission). These infections do not cause disease in the baby unless it is very small and premature or has an impaired immune system.

Prevalence & Individuals at Risk

Risk of Severe Sequelae Due to CMV

About 13 to 28% of infected babies will have symptoms at birth or will develop disabilities, including mental retardation, small head size, hearing loss, and delays in development.

While they have greater exposure to CMV, adults and children in daycare settings are not known to be more susceptible than anyone else.

Individuals at Risk

- CMV-seronegative pregnant women, especially those with children in daycare.
- Those engaging in sexual contact.
- Parents of a child who is shedding CMV.
- The risk of primary CMV infection is very high in teen-aged mothers and the risk of congenital CMV infection in their babies is very high.
- Persons who have not been previously infected and have no antibody to CMV.

Incidence of Severe Sequelae & Handicaps Following Primary Maternal Infection

	Week of gestation		
	4–22	16–27	23–40
Congenital infections	51%	60%	44%
Symptoms at birth	12%	16%	0%
Severe handicaps	29%	0%	0%

Source: Stagno et al., JAMA, 1986

CMV Prevalence

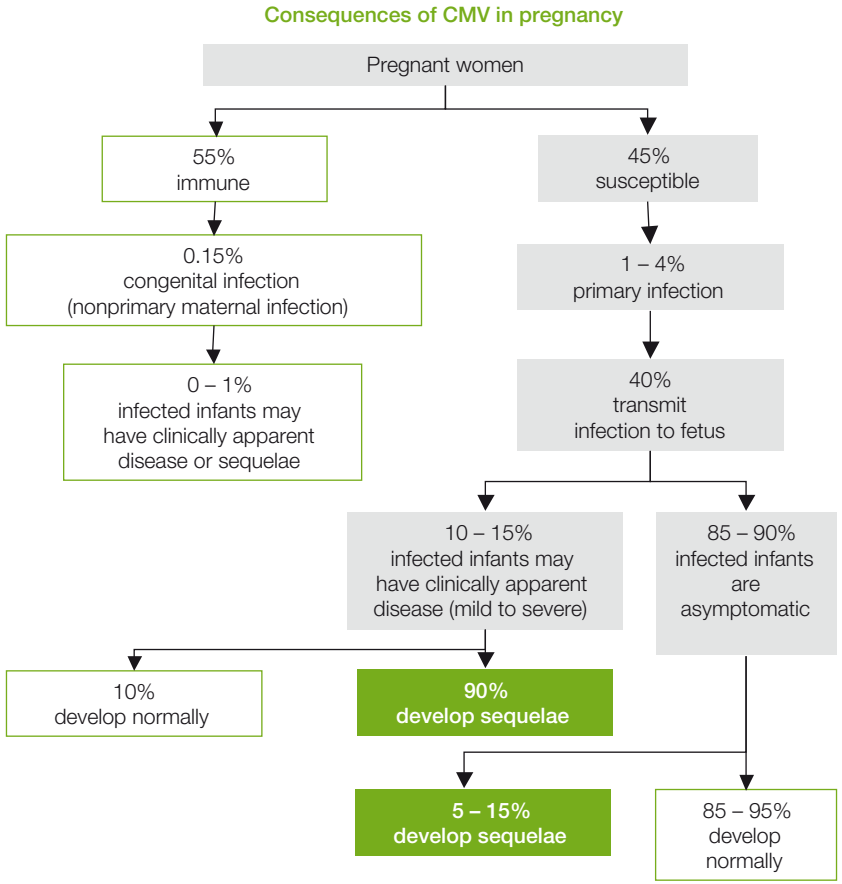
Location	Country	%	Location	Country	%
Freiburg	Germany	42	Houston	USA	79
St. Gallena	Switzerland	45	Buenos Aires	Argentina	81
Paris	France	47	Espírito Santo	Brazil	98
Turku	Finland	54	Jerusalem	Israel	85
Stockholm	Sweden	59	Punjab	India	87
Bologna	Italy	70	Chengdu	China	92
Madrid	Spain	63	Khon Kaen	Thailand	93
Monza	Italy	68	Hong Kong	China	94
Parma	Italy	71	Sendai	Japan	96
Athens	Greece	78	Manila	Philippines	100
Naples	Italy	83	Melbourne	Australia	54
Cosenza	Italy	85	Harare	Zimbabwe	82
Albany	USA	45	Sfax	Tunis	97
Ohio	USA	65	Entebbe	Uganda	100

There exists a wide variation of geographic prevalence rates. The above table underscores the need for CMV education and prevention on a worldwide basis.

The most severe handicaps result from infection acquired during the 4th to 22nd week of gestation.

Diagram of Outcomes

This diagram represents typical infection rates and consequences.



Outcomes in green represent particularly severe sequelae.

Source: Stagno and Whitley, NEJM, 1985

Maternal & Congenital Symptoms

Onset

Although transmission of CMV from mother to fetus may occur at any time during pregnancy, severe neurological complications in the fetus have been reported to occur when a primary infection is diagnosed during the first half of gestation.

Maternal Symptoms

Most cases of maternal CMV infection are asymptomatic. If symptoms develop, they are not specific to CMV, and include fever, headache, fatigue, myalgia, sore throat.

Congenital Symptoms

- Petechiae
- Chorioretinitis
- Hearing loss
- Growth retardation at birth
- Small head size (microcephaly)
- Liver and spleen abnormalities leading to abdominal distention
- Central nervous system abnormalities
- Inguinal hernia
- Fluid collection around the lung or heart

Microcephaly with petechiae

Adverse Outcomes

- Mental retardation
- Sensorineural hearing loss
- Cerebral palsy
- Impaired vision due to chorioretinitis or optic atrophy

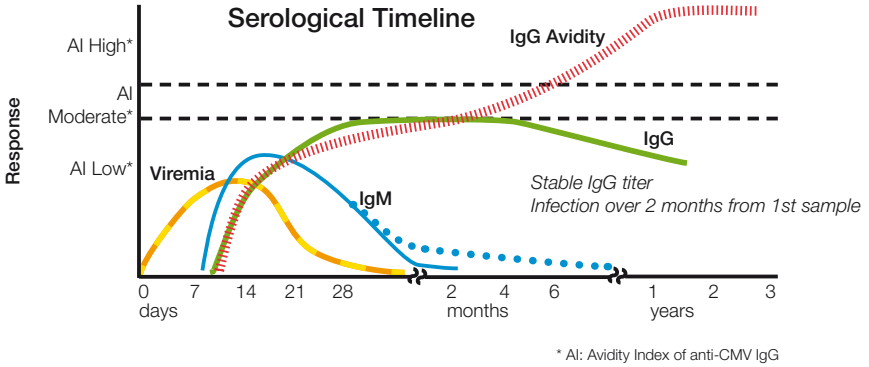
Neuroimaging Abnormalities

- Intracranial calcifications
- Ventriculomegaly
- Cerebral atrophy
- White-matter abnormalities

Laboratory Abnormalities

- Elevation of hepatic transaminases
- Anemia
- Jaundice with direct hyperbilirubinemia
- Low platelet count

CMV Serology



IgG

Detection of CMV-specific IgG is used as a marker of past CMV infection.

IgM

Detection of CMV-specific IgM is used as a marker of active or recent CMV infection.

IgM antibodies are produced during the acute and late phases of a primary CMV infection and may persist for months or years.

A CMV IgM-positive result alone does not accurately predict the risk of fetal infection; a positive IgM test should therefore be considered only as a starting point and a more thorough diagnostic evaluation is necessary to determine whether there is a risk of fetal infection.

IgG Avidity

The IgG avidity assay measures the functional binding affinity of the IgG antibody in response to infection. During the first few weeks following invasion of the host by a pathogen during a primary infection, IgG antibodies of low avidity (low binding affinity) are produced. The avidity of these IgG antibodies increases over time. The maturation of antibody avidity over time can be used at the diagnostic level to discriminate between primary and non-primary infection. CMV IgG antibody of high avidity is detected in subjects with remote or non-primary CMV infection.

Avidity testing should be performed early in gestation; i.e. within the first trimester. A high avidity result later in gestation cannot rule out a primary infection earlier in gestation when low avidity IgG may have been present.

Methods of Testing

Table of Serological Tests & Sample Sources

The following are key questions that drive the use of the diagnostic laboratory:

- 🟠 Has this subject ever had CMV?
- 🟢 Is this a recent primary CMV infection?
- 🟣 Is fetal infection present?
- 🔵 Is congenital CMV infection present in this newborn?

Please use the tables below to find tests that will help you answer these key questions

Sources of samples	Maternal	Fetal
Non-blood	Saliva, urine, cervix secretions used to test for viral shedding	Amniotic fluid used to test for viral shedding by PCR and virus isolation. Most conclusive for fetal infection
Blood	Maternal blood for antigen, DNA and antibody tests	Cord blood for antigen, DNA and antibody tests
Other		Ultrasound detection of abnormalities

Types of serology tests	Maternal	Fetal
IgG antibodies Usually tested in maternal or fetal blood samples Limitations of this test include that it is not conclusive of a latent or active infection	Positive test indicates previous infection, but not active infection 🟠 Should be done pre-pregnancy as a baseline test (if previously negative) indicates infection 🟢	Positive test does not indicate infection
IgM antibodies Marker for both primary and non-primary CMV infection	May persist for nine months after initial infection 🟠 🟢	A CMV IgM-positive result alone is linked to a high risk of fetal infection 🟣 🔵
IgG avidity Measures the functional binding affinity of the IgG class of antibody in response to infection Helps to distinguish between primary and non-primary infection	Acute Phase Reactant (< 4 mos): Low avidity *Low avidity Index: 1–40%* Chronic Phase Reactant (> 4 mos): High Avidity *High Avidity Index: 60–90%* 🟠 🟢	Not tested

Quiz Questions

1. Intrauterine transmission of CMV during a primary CMV infection, especially during which trimester, has the potential to cause significant fetal damage?

A. First trimester
B. Second trimester
C. Third trimester

2. Nonprimary CMV infection is usually characterized by the presence of …?

A. CMV IgM antibodies
B. High avidity CMV IgG
C. Low avidity CMV IgG

3. What environment poses the highest risk of acquiring CMV?

A. Isolated
B. Cleanroom
C. Daycare

4. Is a neonatal CMV IgM-positive result alone linked to a high risk of infection?

A. Yes
B. No

5. Can an IgM-positive antibody test alone differentiate a primary or nonprimary infection in the pregnant woman?

A. Yes
B. No
C. Test is not perfomed

6. "Latency" is the fact that the virus …

A. Persists indefinitely
B. Can be reactivated (to produce infection) by immunosuppression or other stimuli
C. Both A and B

1. A
2. B
3. C
4. A
5. B
6. C

Section 2:

Case Studies

In this section

Learning Objectives

After completing this section, you should be able to:

Describe the different tests used to diagnose maternal and congenital CMV infection.

Understand the use of the CMV algorithm in the diagnosis of CMV infection.

Describe the clinical course of the disease.

Describe measures to prevent maternal and congenital CMV infection.

Indicate the treatment option available for congenital CMV.

Case Study 1:

Non-Primary CMV Infection

A 38-year-old woman in her first pregnancy was referred to the laboratory at 16 weeks of gestation.

Serum collected at 10 weeks gestation was positive for CMV IgG and IgM antibodies. The samples are no longer available.

History-taking revealed the patient had experienced “flu-like symptoms” at the start of pregnancy. Her CMV immune status prior to pregnancy was not known.

Further serologic investigations for CMV were performed at a virology laboratory at 16 weeks gestation with the following results:

Maternal CMV Panel

Assay	Anti-CMV IgG	Anti-CMV IgM	Anti-CMV IgG Avidity
Results	+	+	High

Diagnosis

The IgM-positive and the high avidity index results indicate a nonprimary CMV infection. Despite the presence of IgM antibodies, the high avidity index for IgG antibodies indicate a nonprimary CMV infection.

Prenatal Management

A woman with a nonprimary infection is counselled about the low risk of vertical transmission (0.5% to 2%) and low risk of fetal impairment.

For this reason, amniotic fluid sampling was not proposed, but secondary level follow-up ultrasound scans every four weeks until the end of pregnancy were done to disclose any changes in morphology and fetal growth correlated to congenital CMV infection.

The woman was invited to test the baby within the first two weeks post-birth by means of urine or saliva CMV isolation.

Neonatal Outcome

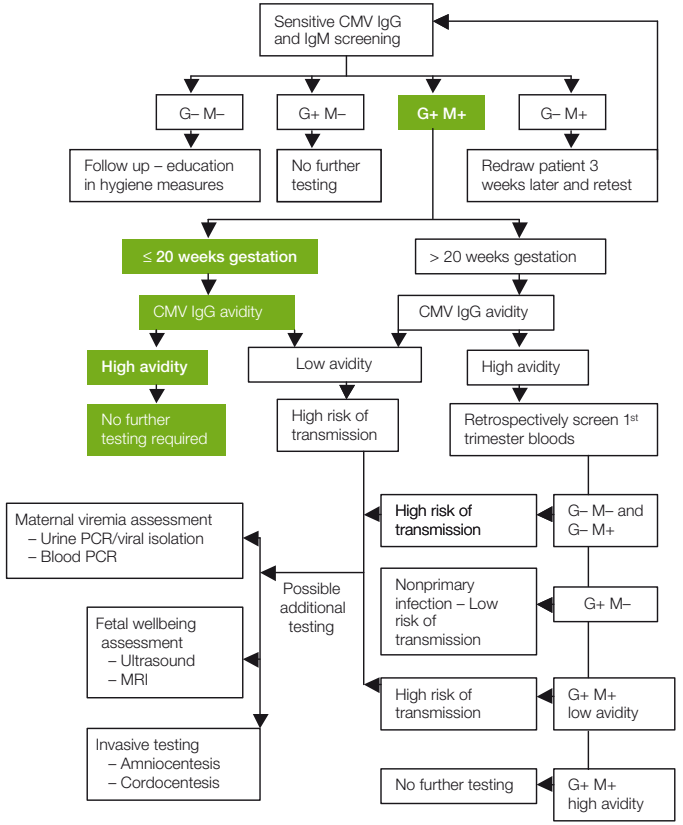
At birth, no clinical evidence of congenital infection was detected, and the urine and saliva cultures for CMV were negative.

Case 1:

Protocol for Management

This diagram represents typical infection rates and consequences.

Diagnostic algorithm for CMV serology screening in pregnant women



Source: Munro et al., J. Clin. Microbiol., 2005

Case Study 2:

Primary CMV Infection

A 35-year-old woman who was at 18 weeks gestation in her third pregnancy had the following history:

At week four, she had persisting lethargy following a flu-like illness with low-grade fever and malaise. At week ten, she tested positive for CMV IgG and borderline positive for IgM antibodies. At week 16, repeat testing confirmed these serologic results.

During her first pregnancy, the patient was not immune to CMV, and during her second pregnancy, she was not tested. She was referred by her physician at 18 weeks gestation to an infectious disease specialist for further evaluation.

The physician ordered the maternal CMV antibody panel with the following results:

Maternal CMV Antibody Panel

Assay	Anti-CMV IgG	Anti-CMV IgM	Anti-CMV IgG Avidity
Results	+	Borderline +/–	Borderline

Maternal Diagnosis

The borderline results for the IgM and avidity tests in light of the previous clinical history suggested a possible recent primary CMV infection.

Maternal CMV PCR Panel

Assay	Maternal Blood	Maternal Urine	Amniotic Fluid
Results	Not tested	Not tested	+ (quantitavely measured)

Next Steps

The next concerns are the potential risk of transmission and harm to the fetus. To determine whether the fetus is infected, prenatal diagnosis is recommended.

At week 21 of gestation, the patient underwent ultrasound-guided trans-abdominal amniocentesis as well as fetal ultrasound studies.

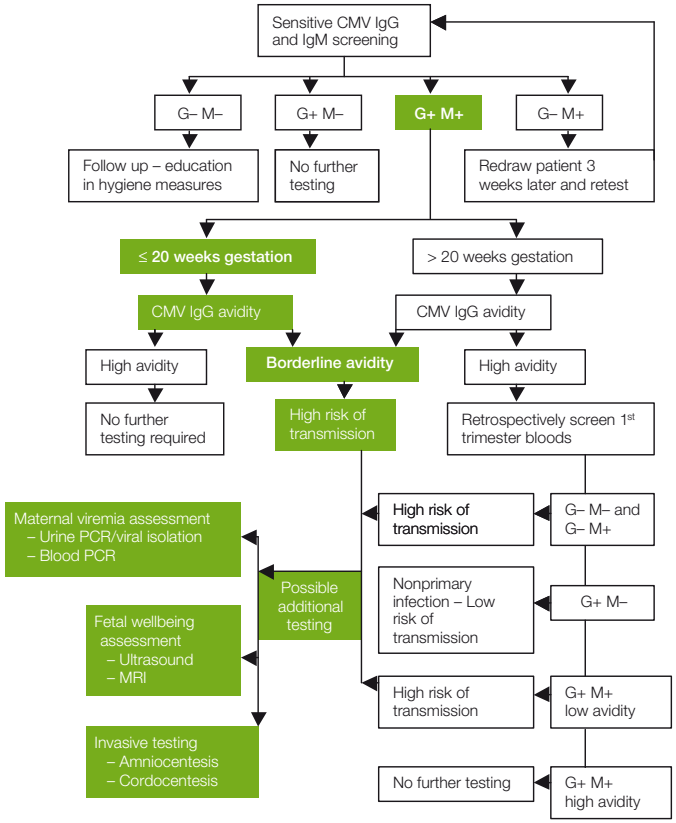
Prenatal Diagnosis

Virologic studies of amniotic fluid were positive. Ultrasonographic examination revealed abnormal intracranial structure and hyperechogenic bowel.

Case 2:

Protocol for Management

Diagnostic algorithm for CMV serology screening in pregnant women



The mother decided to continue with the pregnancy.

At Birth

A male infant was delivered at 39 weeks gestation.

Upon physical examination, the infant appeared well and comfortable. His features were not dysmorphic, and he was not in respiratory distress. He had multiple petechial lesions on his face, trunk, arms and legs. Laboratory assay showed thrombocytopenia, and ophthalmologic investigations were normal.

Saliva and urine collected one day after birth yielded a positive virus isolation.

Quantitative PCR in blood, ultrasound examination of the brain, and cranial computed tomography scanning were all positive. Audiologic testing was normal.

Congenital Symptomatic CMV infection

The newborn had depressed platelet levels, severe cerebral ventriculomegaly, and diffuse microcalcified cerebral areas.

Therapeutic Strategies

Possible treatment options were discussed with the parents who opted to have their infant receive intravenous ganciclovir for six weeks. Therapy was completed without serious complications.

Other Strategies

The newborn will be followed up at 3, 6, 12, and 18 months of life and then annually up to school age. Follow-up includes clinical evaluation, laboratory investigations, neurodevelopmental and psychointellectual assessment, fundus oculi and audiologic assessment.

Case Study 3:

Primary CMV Infection

A 30-year-old woman, who was at 31 weeks of gestation during her fourth pregnancy, consented to have her blood tested for CMV antibodies during a glucose tolerance test.

Below are the results:

Maternal CMV Antibody Panel

Assay	Anti-CMV IgG	Anti-CMV IgM	Anti-CMV IgG Avidity
Results	+	+	Low

Initial Diagnosis

This woman was initially diagnosed as having a primary CMV infection.

The physician ordered CMV antibody tests on a blood specimen donated earlier during gestation with the following results:

Maternal CMV Antibody Panel (early test)

Assay	Anti-CMV IgG	Anti-CMV IgM	Anti-CMV IgG Avidity
Results	–	–	Not tested

Confirmation of Primary Infection

These results document that CMV seroconversion occurred during gestation, confirming recent primary CMV infection in the pregnant woman.

Next Steps

The physician then ordered the following additional PCR tests on the woman to determine if the actual CMV virus was present with the following results:

No amniotic fluid was collected because of the late gestational age at the time of the examination.

Maternal CMV PCR Panel

Assay	Maternal Blood	Maternal Urine	Amniotic Fluid
Results	+	+	Not tested

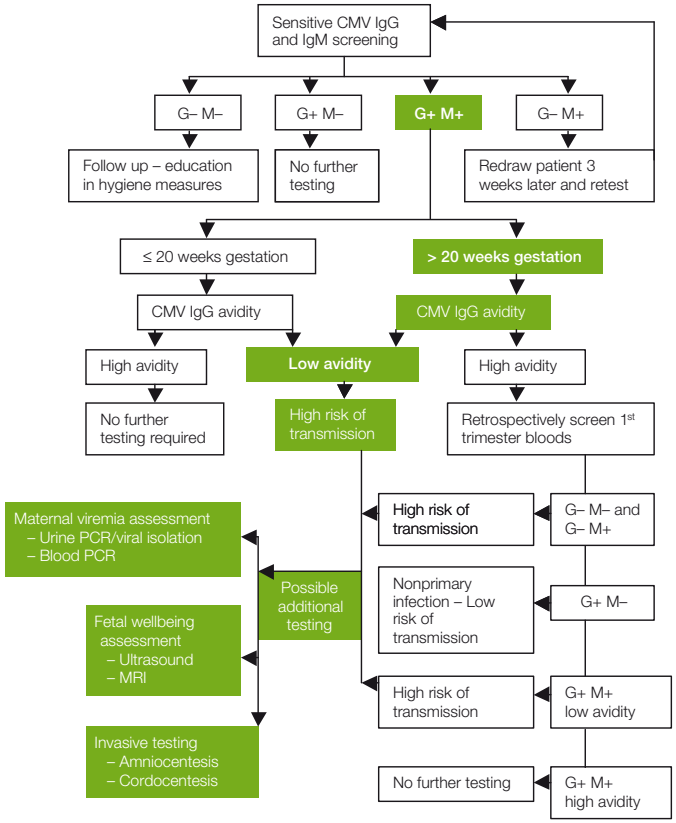
Congenital Risk Confirmed

These results confirm that the virus was present and that the developing fetus was at risk for congenital CMV infection.

Case 3:

Protocol for Management

Diagnostic algorithm for CMV serology screening in pregnant women



At birth, the neonate presented no symptoms of CMV disease.

Next Steps

Since the mother had a primary CMV infection during gestation, the physician ordered the following tests on the neonate within two weeks of birth to determine if intrauterine transmission of the virus had occurred.

The following are the results:

Neonatal CMV Panel

Assay	CMV PCR Blood	CMV PCR Urine	CMV Isolation Urine
Results	+	+	+

Neonatal Diagnosis

The neonate tested positive for CMV virus thus establishing the diagnosis of congenital CMV infection.

The neonate had a normal hearing test upon discharge from the hospital and was enrolled in subsequent hearing tests to monitor for sensorineural hearing loss.

Prevention & Treatment

Prevention

Although no actions can totally eliminate all risks of catching CMV, precautionary measures can be taken to help control to spread of infection in the home and in other settings.

Prevention of congenital CMV is the major driving force for the development of a vaccine.

Steps to Take

- Always wash hands after changing diapers.
- Avoid kissing young children on the mouth.
- Sanitize the toys of children, and be aware when you touch unsanitized toys.
- Do not share food, drinks, or utensils with young children.

Photo courtesy Buzztone

Intervention and Treatment

At the present time the only intervention available for fetal CMV infection is termination of pregnancy. Careful use of prenatal maternal and fetal diagnoses should reduce the likelihood that termination of pregnancy will be chosen when there is no evidence of fetal damage.

Preliminary evidence suggests that CMV hyperimmunoglobulins may reduce the risk of transmission to the fetus but more studies are needed.

Also, a recent case study has shown the successful use of oral ganciclovir to treat intrauterine CMV infection in a pregnant renal transplant recipient.

Only ganciclovir has been evaluated in the treatment of infants with disease symptoms.

- Ganciclovir improves hearing or prevents hearing deterioration up to 6 month of age compared with no treatment.
- Ganciclovir reduces the risk of worsening of hearing up to and beyond one year of age.
- Ganciclovir did not change the course of the acute illness (clinical or laboratory) in symptomatic newborns.
- Neutropenia was seen in 2/3 of Ganciclovir recipients requiring dose adjustment in about half.

Quiz Questions

1. CMV transmission risk can be lowered by washing hands thoroughly.

A. Yes
B. No

2. Children's toys can be contaminated with CMV.

A. Yes
B. No

3. Ganciclovir can be used to treat infants.

A. True
B. False

A .3
A .2
A .1

References

Lazzarotto T. et al. (2004) Congenital cytomegalovirus infection: recent advances in the diagnosis of maternal infection. Human Immunol. 65: 410-415.

Munro S.C. et al. (2005) Diagnosis of and screening for cytomegalovirus infection in pregnant women. J. Clin. Microbiol. 43: 4713-4718

National Congenital CMV Disease Registry. Baylor College of Medicine, Texas Children's Hospital. http://www.bcm.edu/pedi/infect/cmv/cmvbroch.htm

Nigro, G. et al. (2005) Passive immunization during pregnancy for congenital cytomegalovirus infection. N. Eng. J. Med. 353:1350-1362.

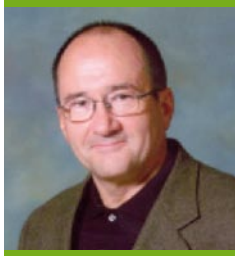
Puliyanda, D.P. et al. (2005) Successful use of oral ganciclovir for the treatment of intrauterine cytomegalovirus infection in a renal allograft recipient. Transpl. Infect. Dis. 7:71-74.

Stagno S. and Whitley RJ. (1985) Herpesvirus infections of pregnancy. Part I: Cytomegalovirus and Epstein-Barr virus infections. New Eng. J. Med. 313: 1270-1274

Stagno S. et al. (1986) Primary Cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. J. Amer. Med. Assoc. 256: 1904-1908

U.S. Census Bureau, Population Division, Fertility & Family Statistics Branch, Who's Minding the Kids? Child Care Arrangements: Spring 1999 (PPL-168) http://www.census.gov/population/www/socdemo/child/ppl-168.html

About the Authors



Robert F. Pass, MD

Robert F. Pass is a Professor of Pediatrics and Microbiology at the University of Alabama at Birmingham School of Medicine. He has studied the epidemiology, natural history and diagnosis of maternal, and congenital Cytomegalovirus infections for many years. He is currently conducting clinical trials of a recombinant, subunit vaccine aimed at prevention of maternal and congenital Cytomegalovirus infection.

Maria Paola Landini, MD, PhD

Professor Maria Paola Landini, MD PhD, is the Dean of the Medical School of the University of Bologna as well as the Director of the Clinical Unit of Microbiology at St. Orsola Malpighi General Hospital.

Since her PhD thesis in 1981 she has published more than 160 scientific papers on different aspects of viral infections, of which human Cytomegalovirus (CMV) has been her major research interest. She has made significant contributions in the following areas: identification and localization of CMV structural polypeptides; immune response to CMV structural and non-structural proteins; production, characterization and use as diagnostic tools of CMV antigens produced in bacteria via genetic engineering; study of CMV gene function; study on the prenatal and postnatal diagnosis of congenital CMV infection.

Tiziana Lazzarotto, PhD

Tiziana Lazzarotto, PhD, is the head of the Laboratory of Virology at St. Orsola Malpighi General Hospital, University of Bologna with three main areas of focus: Herpes Viruses and Adenovirus, CMV infections and diagnosis of respiratory viruses, enteroviruses and viral gastroenteritis.

Since her thesis she has published more than 60 scientific papers on human Cytomegalovirus infection, especially immune response to CMV structural and nonstructural proteins; study of the avidity of CMV IgG and the use of avidity tests in identification of pregnant women at risk of transmitting congenital infection; study on the prenatal diagnosis of congenital CMV infection.

Toxoplasma gondii

Contents

Introduction

Toxoplasma gondii (T. gondii) is a protozoan parasite that can cause the disease toxoplasmosis in humans and animals. One of the tragic consequences of *T. gondii* infections in humans occurs when women contract the infection during gestation and pass the parasite to their unborn child.

T. gondii can cause devastating disease in the fetus and newborn, yet remain unrecognized in women who initially acquired the infection during pregnancy. Furthermore, in many countries, infection in the neonate is not diagnosed in a timely manner, thereby precluding therapeutic intervention which could prevent subsequent development of serious sequelae of the infection. Such sequelae include: decreased vision or blindness and mental and psychomotor retardation.

The healthcare cost estimates for special care of children with congenital toxoplasmosis has been estimated to extend into the hundreds of millions of dollars (US$) annually.

Immunocompromised patients, including bone marrow and solid organ transplant recipients and AIDS patients, are also at risk for devastating disease outcomes. Toxoplasmosis is a significant cause of morbidity and mortality in immunodeficient patients.

T. gondii is usually contracted by consumption of raw or undercooked meat or contaminated water. Contact with cat feces contaminated with oocysts is also a risk factor for infection. Infection is lifelong and can happen to anyone.

Nevertheless, *T. gondii* infection in humans is detectable and preventable.

This learning guide will highlight the key features of maternal and congenital *T. gondii* infection, review methods of detection, and describe effective steps toward prevention of infection.

Section 1:

The Biology & Pathology of *T. gondii*

In this section

Learning Objectives

After completing this section, you should be able to:

Explain why *T. gondii* infection is dangerous in pregnant women.

Indicate how *T. gondii* is transmitted.

Name the major risk factors for acquiring a *T. gondii* infection.

Identify individuals at risk for severe consequences of *T. gondii* infection.

Describe the symptoms and clinical course of the disease.

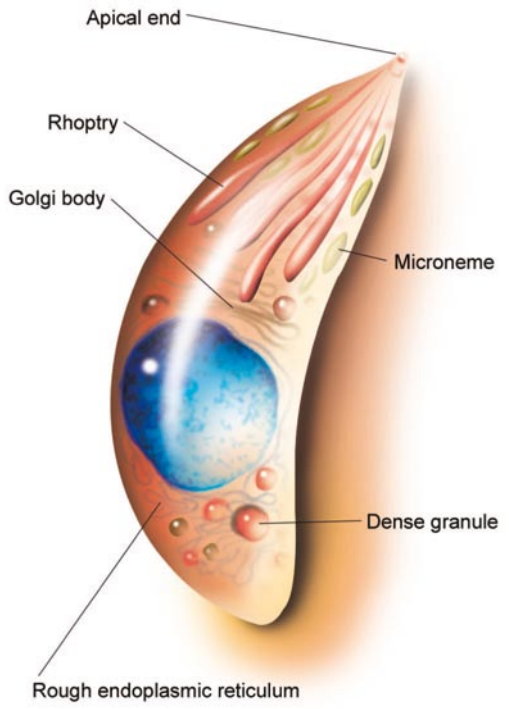
Describe ways of preventing infection.

What is *Toxoplasma gondii*?

Toxoplasma gondii (T. gondii) was first recognized as a cause of disease in humans in 1937, when it was found to be the cause of death in an infant with encephalitis. Thereafter, descriptions of *T. gondii* as a cause of fetal infection and of neonatal infant death established the parasite as a cause of congenitally transmitted disease.

The first cases in adults were described in 1940. Following development of a serologic test in 1948, the parasite was noted to be widespread in nature among animals, birds, and humans.

During the ensuing years, the importance of the infection – when acquired by a woman during gestation, and the tragic outcome that could occur in her offspring – served as an impetus for investigators to gain an understanding of the epidemiology of the infection in pregnant women, the clinical spectrum of disease that it causes, and of methods for diagnosis and management of the acutely infected pregnant woman and her infant.



Toxoplasma gondii

Biology & Pathology

Toxoplasma gondii is a species of parasitic protozoa that can cause the disease toxoplasmosis in humans. *T. gondii* exists in three forms: tachyzoite, cyst, and oocyst.

Tachyzoite

The tachyzoite form is found in the acute infection stage, and can invade all mammalian cells, excluding red blood cells.

It multiplies intracellularly, destroys its host cell, and goes on to invade other cells by spreading throughout the body via the bloodstream.

Cyst

The cyst form is found in multiple tissues (e.g. skeletal and heart muscle, central nervous system) following the acute infection, and may persist for years or, perhaps, for life.

The cyst form derives from tachyzoites that convert to the encysted form within the host cell. Cysts are formed early during the acute infection, then persist in the human body for life. In otherwise normal individuals, the cyst form is not associated with an inflammatory response and has not definitively been shown to be associated with disease states.

This form of the parasite is found in muscles of animals from which we obtain our meat. Upon exposure to peptic or tryptic digestive fluid, the cysts rupture and the intracystic parasites go on to invade and spread throughout the body as tachyzoites.

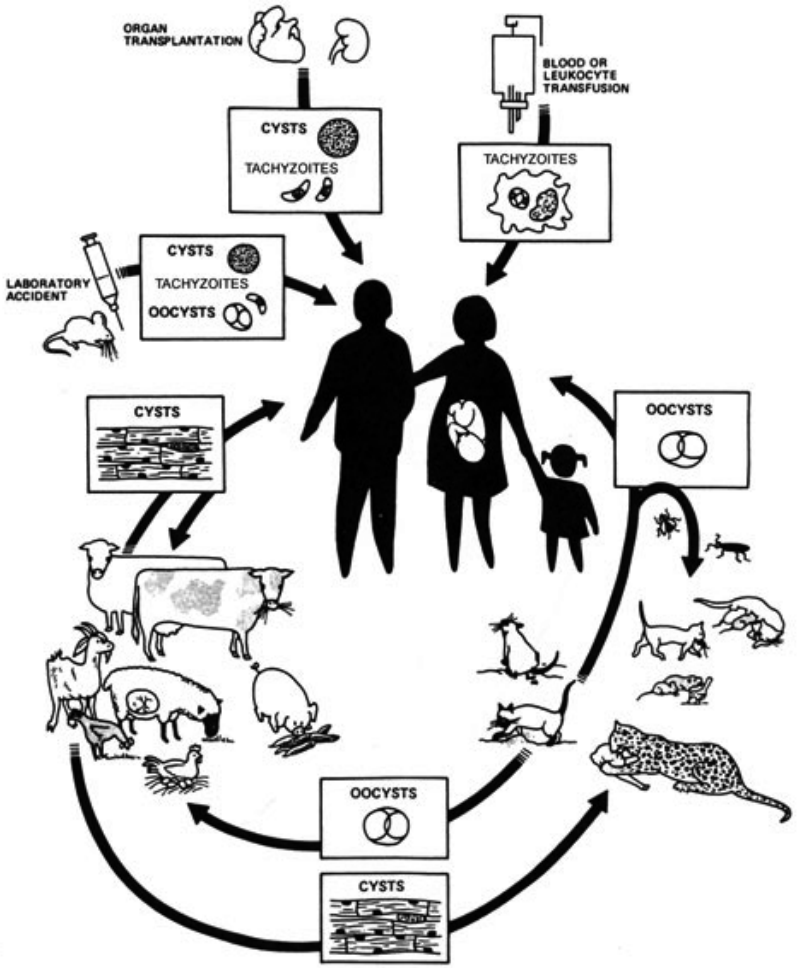
The cyst form is killed by desiccation, by heating above 66 degrees C (150.8 deg F), and by freezing at minus 20 degrees C (–4 deg F) for 18 to 24 hours, followed by thawing.

Oocyst

The oocyst results from sexual forms of the parasite that occur intracellularly solely in the small intestines of members of the cat family.

Oocysts may become infectious as early as 1–2 days after excretion in the feces of acutely infected cats and can remain infectious for months, or years, under most ordinary environmental conditions. Infectious oocysts can be killed by exposure to boiling water for 5 minutes.

The Lifecycle of *T. gondii*



Source: Remington J.S. et al. (2005) Toxoplasmosis

Routes of Transmission

Undercooked meat is the greatest risk factor for infection in the United States and Europe.

T. gondii is also transmitted to humans and other mammals and birds (secondary hosts) via contamination with infected feces from members of the cat family (primary hosts).

Situations in which transmission of *T. gondii* often occurs include:

Contact With Fecal Matter

- Contact with cat feces contaminated with oocysts
- Gardens
- Sandboxes
- Cat litter

Undercooked meat is the greatest risk factor for infection in the United States and Europe.

Ingestion

- Contaminated foods
- Raw and undercooked meat
- Raw, unwashed vegetables
- Raw, unwashed fruits
- Contaminated water

Intrauterine Transmission

- *T. gondii* can be transmitted from mother to fetus, resulting in congenital infection.

Transplants or Transfusions

- Accidental needle sticks
- Organ transplant recipients

Risk of transmission increases when parasites are allowed to contact mucosal surfaces.

Ownership of a cat is not a direct risk factor.

Individuals at Risk

There are four groups of individuals at risk for serious outcomes resulting from infection:

1 **Seronegative pregnant women who acquire the infection during gestation.**

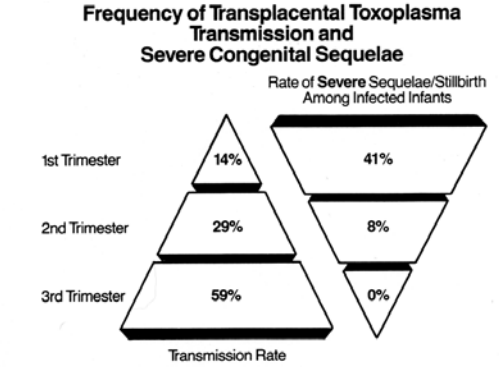
The likelihood and severity of intrauterine infection depends on when during the pregnancy the mother is infected.

2 **Fetuses of women who acquire the infection during gestation.**

3 ***Toxoplasma* seronegative or seropositive immunocompromised patients.**
(e.g. those with hematologic malignancies, lymphoproliferative disorders, AIDS, those on high dose immunosuppressive therapy)

Patients in group 3 are at risk from both the acute acquired infection, as well as from recrudescence of a previously latent infection (cyst form).

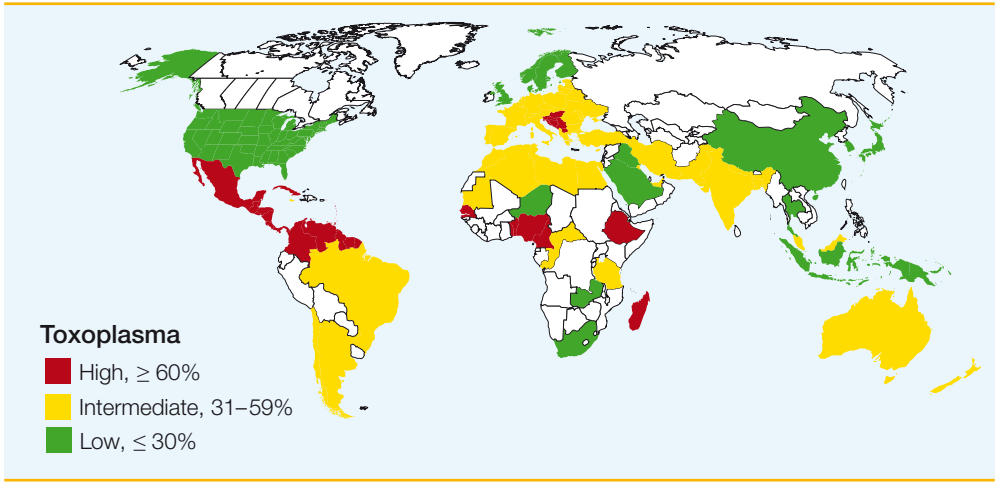
4 ***Toxoplasma* seronegative organ transplant recipients who are transplanted with an organ from a seropositive donor.**



Source: Desmonts and Couvreur, Ann. Pediatr., 1984

Incidence & Prevalence

T. gondii is ubiquitous in nature and is a common infection of humans worldwide.



The map of Toxoplasma prevalence generalizes available data, patterns may vary within countries

Unfortunately, at present, we do not have accurate figures for the prevalence/incidence of congenital *T. gondii* infection or congenital toxoplasmosis in the United States. In a recent study in the United States, it was estimated that the incidence in seronegative pregnant women is 0.27%. If one were to use an overall transmission rate of 33%, and with a cohort of the approximately 4 million births in the United States, approximately 3500 infants with congenital toxoplasmosis would be born each year (in France it is approximately 600).

The prevalence of the infection increases with age, and most studies have not reported a significant difference in prevalence between the sexes.

Among women in the childbearing population in the United States, there has been a dramatic decrease in seropositivity over the past 30 years.

There may be considerable differences in prevalence between populations within a given locale.

For example, there is a marked difference between the childbearing population of Hispanic and non-hispanic women in Los Angeles, California and between different ethnic groups in many nations in Western Europe.

Cultural habits in regard to cooking of food is likely the major cause of differences in the frequency of infection with *T. gondii* in many areas of the world.

Considerable differences are noted in prevalence figures between different geographical areas (see map). It varies from less than 10% to almost 80%.

As a consequence of the considerable differences in prevalence of the infection among general populations, there are large differences in the incidence of congenital infection. It can vary from 1:1000 live births, as is the case in France, to 1:10,000 in countries with a lower prevalence of infection.

Disease Symptoms

Acquired *T. gondii* infection in the otherwise immunologically normal individuals most often is not recognized clinically by the patient.

Non-Specific Symptoms

Acute infection may be associated with non-specific symptoms:

- Slight fever
- Aches/Pains
- Swollen lymph nodes
- Fatigue
- Rash (rarely)
- Eye infection (posterior uveitis)

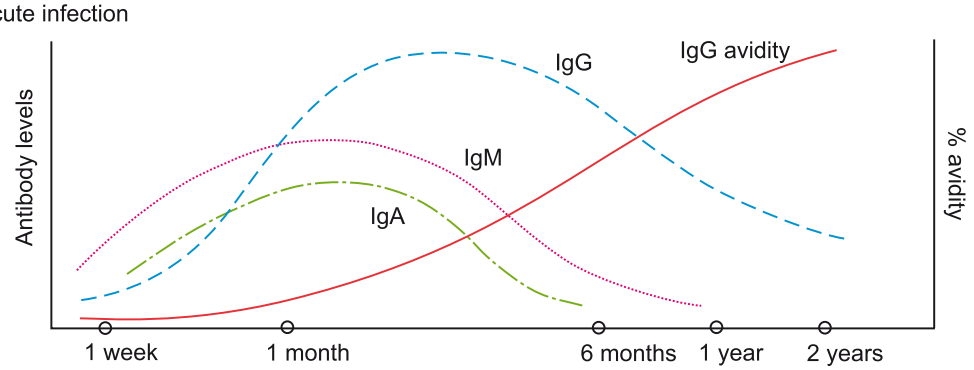
Lymphadenopathy

The most common clinically-recognized manifestation is swollen lymph nodes, said to occur in approximately 10% of acutely infected persons:

- Most often localized to cervical (neck) region as a solitary, non-tender lymph node, without associated pus formation.
- May include the inguinal, axillary, or supraclavicular areas and may be mistaken clinically with infectious mononucleosis.
- Lymphadenopathy has also been noted in the peripectoral area where it may raise the suspicion of a tumor in the breast.
- Diagnosis may be made at lymph node biopsy by demonstration of characteristic histologic features. Serologic test results revealing recently acquired infection in the presence of lymphadenopathy are highly suggestive of *T. gondii* as the cause.

Toxoplasma Serology

Standard Serology for Toxoplasmosis



IgG

T. gondii-specific IgG antibodies are produced throughout life after infection.

Detection in a single sample at any titer with any test proves only that infection has been acquired at some time in the past.

IgM

IgM antibodies are detected in individuals with a recently acquired infection, but they may persist for one year or longer.

False-positive reactions may be found in some patients who have never been infected by *Toxoplasma* (in such individuals, tests for specific IgG remain negative).

IgG Avidity

The measurement of specific-IgG avidity is particularly helpful when both IgG and IgM tests are positive on a first serum sample drawn during pregnancy.

A high avidity test result rules out an infection acquired in the preceding 3 to 5 months (the exclusion period varies according to the kit used), but a low-avidity result may persist for one year.

Low avidity test results cannot be used to diagnose an acute toxoplasmosis.

Methods of Testing

The following are key questions that drive the use of the diagnostic laboratory:

- Has this subject been infected with *T. gondii*?
- Can an acute *T. gondii* infection be excluded?

Please use the table below to find tests that will help you answer these key questions

Laboratory Diagnostic Tests	
Serologic	Because the signs and symptoms of toxoplasmosis are non-specific and because most cases are subclinical, the diagnosis is based on serological tests
Sabin-Feldman Dye Test (IgG)	Test is based on the observation that when living organisms are incubated with normal serum, they become swollen and stain blue when methylene blue is added to the suspension Living parasites exposed to antibody-containing serum, under the same conditions, appear thin, distorted, and are not stained when the dye is added
IgG	*T. gondii*-specific IgG antibodies are produced throughout life after infection Detection in a single sample at any titer with any test proves only that infection has been acquired at some time in the recent or distant past
IgM	IgM antibodies are detected in individuals with the recently acquired infection They may persist for one year or longer False-positive reactions may be found in chronically infected individuals or in some patients who have never been infected by *T. gondii* (in such individuals, tests for specific IgG remain negative)
IgG Avidity Assay	The measurement of specific-IgG avidity is particularly helpful when both IgG and IgM tests are positive on a first serum sample drawn during pregnancy A high avidity test result rules out an infection acquired in the preceding 3 to 5 months (the exclusion period varies according to the kit used) but a low or equivocal avidity result may persist for as long as one year or more Low avidity or equivocal test results should not be used to diagnose acute infection
AC/HS	Differential agglutination test compares titers obtained with formalin-fixed tachyzoites (HS antigen) with those obtained with acetone- or methanol-fixed tachyzoites (AC antigen) The AC antigen preparation contains stage-specific antigens that are recognized by IgG antibodies early during infection; these antibodies have different specificities than those found later in the infection AC/HS should be used with other serum tests Available only at Toxoplasma Reference Laboratory, Palo Alto Medical Foundation and Institut de Puériculture, Paris
Biopsy	In some patients a lymph node biopsy may be necessary to look for characteristic histologic features of *T. gondii* infection and to rule out lymphoma

Quiz Questions

1. *T. gondii* results in particularly severe sequelae in the congenitally-infected fetus when acquired for the very first time by the mother in the:

A. First trimester
B. Second trimester
C. Third trimester

2. What visual clue tells you that you have killed all *T. gondii* from meat that you are cooking?

A. Cooked to a “medium” specification, partially pink
B. Cooked to a “medium-well” specification, lightly pink
C. Cooked to a “well-done” specification, fully-cooked without any pink

3. Is it recommended and prudent to have someone else change the kitty litter while you are pregnant or attempting to conceive?

A. Yes
B. No

4. How long is *T. gondii* IgG detectable after the first acute infection?

A. 60 days
B. 1 year
C. For life

5. The most common clinically recognized manifestation is lymphadenopathy.

A. Yes
B. No

1. A
2. C
3. A
4. C
5. A

Section 2:

Case Studies

In this section

Learning Objectives

After completing this section, you should be able to:

Describe symptoms of *T. gondii* infection.

Interpret *T. gondii* serologic test results.

Case 1:

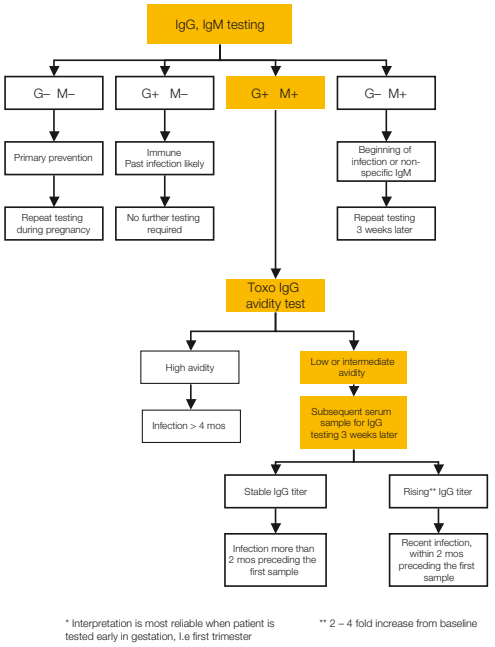
Late (Third Trimester) Detection

A 27-year-old pregnant woman visited her physician after noticing development of a "lump" on her left neck at approximately 24 weeks of gestation. A biopsy revealed characteristic histologic features of toxoplasmic lymphadenopathy.

Her physician then requested serologic testing for *T. gondii*. Her serologic results at week 31 of gestation are shown:

Dye Test	IgM	AC/HS	Avidity
+	+	Acute pattern	Low avidity

T. gondii Serologic Diagnostic Algorithm*



* Interpretation is most reliable when patient is tested early in gestation, I.e first trimester

** 2 – 4 fold increase from baseline

Diagnosis
Toxoplasmosis in the third trimester.

Prenatal Management

The patient was placed on pyrimethamine, sulfadiazine, and folinic acid. She was well beyond the first trimester during which pyrimethamine may interfere with embryonic development and, therefore, is not used.

Attempt at diagnosis in the fetus is recommended, so treatment of an infected infant can begin as soon as possible after of birth. Barring contraindication and after informing the patient of the potential hazards, amniocentesis followed by PCR on the amniotic fluid can be used to diagnose infection in the fetus.

Case 2:

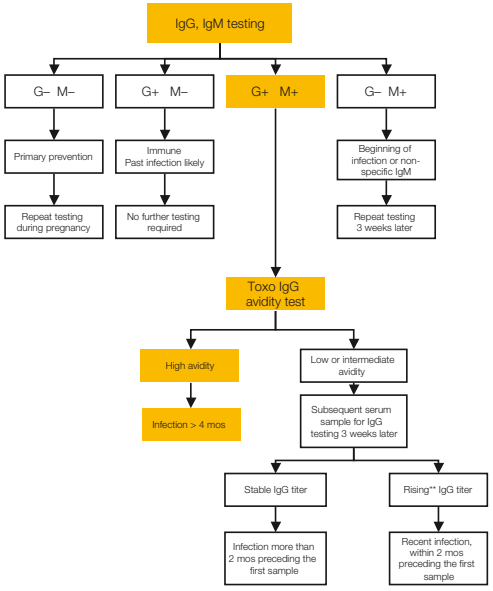
Infection Prior to Gestation

A 32-year-old pregnant female had *Toxoplasma* serology performed at 14 weeks gestation.

The results are shown:

Dye Test	IgM	AC/HS	Avidity
+	+	Not tested	High

T. gondii Serologic Diagnostic Algorithm*



* Interpretation is most reliable when patient is tested early in gestation, i.e first trimester

** 2 – 4 fold increase from baseline

Diagnosis

No other serologic tests were requested by her physician. We can not determine when she became infected. IgM antibodies may persist for over a year and their duration does not correlate with titer in the Dye test. The testing revealed high avidity antibodies were present, suggesting that infection occurred prior to gestation.

Case 3:

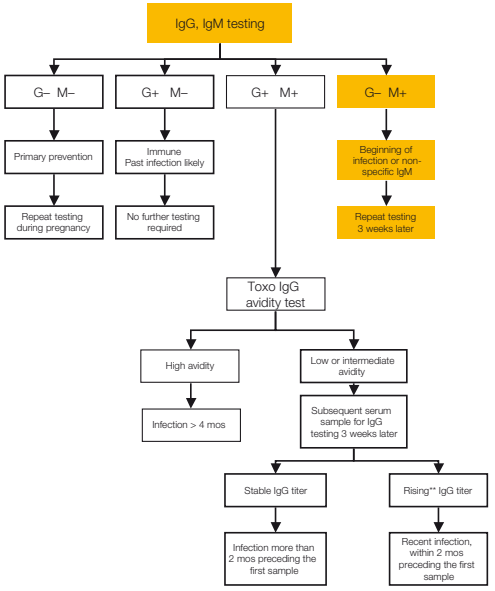
False-Positive Result

A 28-year-old pregnant female had *Toxoplasma* serology performed at 12 and 15.5 weeks gestation.

The results are shown:

Week of gestation	Dye Test	IgM	AC/HS	Avidity
12	–	+	Not tested	Not tested
15.5	–	+	–	Not tested

T. gondii Serologic Diagnostic Algorithm*



* Interpretation is most reliable when patient is tested early in gestation, i.e first trimester

** 2 – 4 fold increase from baseline

Diagnosis at Week 12

At 12 weeks gestation, other serologic tests were requested by her physician. We can not determine when she became infected. The IgM test result may reflect a very recently acquired infection (during which the Dye Test titer did not detect IgG antibody) or a not uncommon false-positive IgM test titer.

Diagnosis at Week 15.5

Three and a half weeks later, further testing revealed a negative Dye Test, a positive IgM test, and a negative AC/HS test, indicating that the patient was not infected.

Prevention & Management

Prevention

Infection with *T. gondii* and congenital toxoplasmosis are preventable. In those countries where there is no systematic serologic screening program, education is the principal means of prevention.

Prospective Mothers

Women contemplating pregnancy should be tested for *Toxoplasma* antibodies. Seronegative women should follow guidelines for non-immune pregnant women listed below.

Non-Immune Pregnant Women

- Cook meat to well-done (not pink in the center).
- Avoid touching mucous membranes of mouth and eyes while handling raw meat.
- Wash hands thoroughly after handling raw meat.
- Clean kitchen surfaces that come into contact with raw meat.
- Wash fruits and vegetables thoroughly before consumption.
- Prevent access of flies and cockroaches to fruits and vegetables.
- Practice thorough hand washing with soap.
- Ask someone else to handle kitty litter and disinfect litter boxes for 5 minutes with near-boiling water.
- Avoid children's sand boxes.
- Wear gloves when gardening.

Fetuses

Identify women at risk by serologic testing and perform prenatal counseling.

Treatment during pregnancy has been stated to result in a 60–70% prevention rate of congenital infection.

If recently acquired infection cannot be excluded in the pregnant women and depending on the week of gestation, a treatment regimen of either spiramycin or a combination of pyrimethamine/sulfadiazine/leucovorin can be given to attempt prevent congenital infection.

Eat well-cooked meat.

Quiz Questions

1. Pyrimethamine is potentially teratogenic and, therefore, is not used in the:

A. First trimester
B. Second trimester
C. Third trimester

2. PCR on the amniotic fluid can be used to diagnose infection in the fetus?

A. Yes
B. No

3. What would prompt an IgG avidity test?

A. G+ M–
B. G+ M+
C. G– M+

4. Initial *Toxoplasma* serology is most optimally performed during which trimester of pregnancy?

A. First trimester
B. Second trimester
C. Third trimester

5. Could vegetables from your garden have *T. gondii* on the surface?

A. Yes
B. No

1. A
2. A
3. B
4. A
5. A

References

Cozon, G.J., Ferrandiz, J., Nebhi, H. et al. (1998) Estimation of the avidity of immunoglobulin G for routine diagnosis of chronic *Toxoplasma gondii* infection in pregnant women. Eur. J. Clin. Microbiol. Infect. Dis. 17:32-36

Dannemann, B.R., Vaughan, W.C, Thulliez, P. and J.S. Remington (1990) Differential agglutination test for diagnosis of recently acquired infection with *Toxoplasma gondii*. J. Clin. Microbiol. 28:1928-1933

Desmonts G. and Couvreur J. (1984) Ann. Pediatr. 31: 805

Hohlfeld, P., Daffos, M., Costa, J.M. et al. (1994) Prenatal diagnosis of congenital toxoplasmosis with a polymerase chain reaction test on amniotic fluid. N. Engl. J. Med. 331:695-699

Montoya, J.G. (2002) Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. J. Infect. Dis. 185(Suppl 1):S73-82

Pfrepper, K.I., Enders, G., Gohl, M. et al. (2005) Seroreactivity to and avidity for recombinant antigens in toxoplasmosis. Clin. Diagn. Labora. Immunol. 12:977-982

Remington, J.S. et al. Toxoplasmosis, in Remington, J.S., Klein, J.O. (eds.) (2005) Infectious diseases of the fetus and newborn infant, 6th edition, Philadelphia, W.B. Saunders

Tissot-Dupont, D., Fricker-Hidalgo, H., Brenier-Pinchart, M.P. et al. (2003) Usefulness of western blot in serological follow-up of newborns suspected of congenital toxoplasmosis. Eur. J. Clin. Microbiol. Infect. Dis. 22:122-125

About the Authors

Dr. Thulliez is head of the Toxoplasmosis Laboratory at the Institut de Puériculture de Paris, France.

Dr. Remington is Professor of Medicine at the Stanford University School of Medicine in the Division of Infectious Diseases and Geographic Medicine and is the Marcus A. Krupp Research Chair and Chairman of the Department of Immunology and Infectious Diseases at the Research Institute, Palo Alto Medical Foundation, Palo Alto, California.

Philippe Thulliez, MD

Dr. Thulliez has been working on the diagnosis of Toxoplasma infection in pregnant women, fetuses, and newborn infants for 20 years. He is the co-author of over 100 peer-reviewed papers and has made significant contributions to the improvement of serological methods used for the diagnosis of toxoplasmosis during pregnancy. His laboratory was the first one to develop a procedure for the prenatal diagnosis of congenital toxoplasmosis and has contributed to studies on the clinical follow-up and treatment of congenitally infected children. In addition to his studies in humans, he continues to perform epidemiological studies in animals.

Jack S. Remington, MD, FACP, FRCP

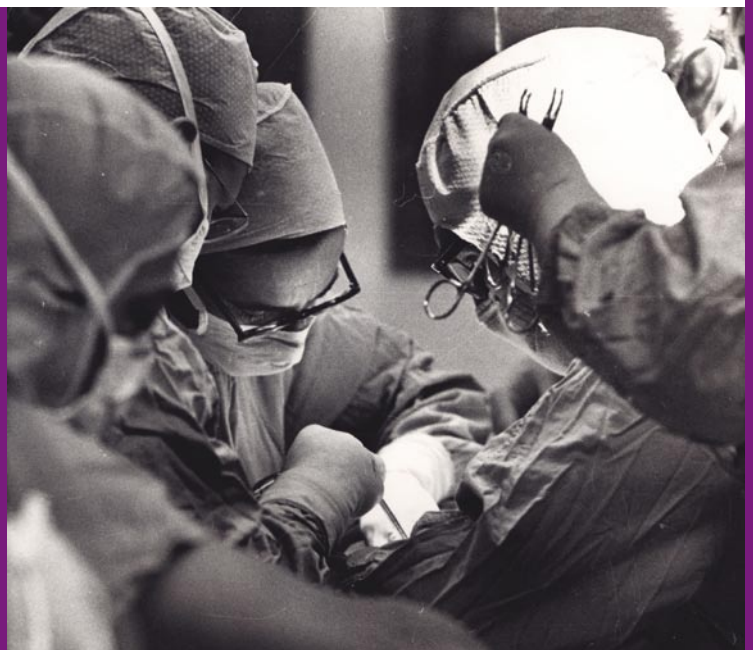
He has served as President of the Infectious Diseases Society of America and the International Immunocompromised Host Society as well as on numerous editorial boards and is an editor of the books, *Current Clinical Topics in Infectious Diseases, Infectious Diseases of the Fetus and Newborn Infant, In Defense of the Brain,* and *New Concepts in the Immunopathogenesis of CNS Infections.*

The author or co-author of over 650 peer-reviewed papers and 15 international patents, Dr. Remington has received numerous awards in recognition of his contributions to medicine and science including distinguished awards from France, UK and Germany as well as the Distinguished Career Achievement Award from the International Immunocompromised Host Society, the Albion Walter Hewlett Award from Stanford University, and the Stanford University School of Medicine Kenneth L. Vosti, M.D. Infectious Diseases Teaching Award.

His group has focused on mechanisms of host resistance against opportunistic pathogens, with special emphasis on *Toxoplasma gondii* and toxoplasmosis. Since the beginning of the epidemic of AIDS, his laboratory has worked on the immunopathogenesis of toxoplasmic encephalitis, particularly the roles of cellular immunity and cytokines. In addition, his group has performed extensive studies on both diagnosis and treatment of the infection in both immunologically normal and impaired individuals.

Maternal & Congenital Rubella

Contents



Introduction

The name Rubella is derived from Latin, meaning “little red.” An infection with Rubella virus manifests as “German measles,” a common, usually benign, exanthematous disease which occurs in the unimmunized.

Rubella infection during the first trimester of pregnancy assumes considerable clinical concern. Placental transmission of Rubella virus to the fetus at this stage frequently results in Congenital Rubella Syndrome (CRS). CRS is characterized by persistent infection of the fetus, with significant adverse effects of purpura, exanthematosis, pneumonia, hepatitis, meningeoencephalitis and congenital malformations of the heart, eye, and ear.

In approximately 2/3 of Rubella virus infections during pregnancy, infants are eventually born without apparent malformation. Nevertheless, a subgroup may develop late-onset disease, with hearing and vision disturbances, mental retardation, autoimmune disorders, and endocrinopathies.

Although the incidence of CRS has declined considerably as a consequence of Rubella vaccination, Rubella infections during pregnancy still occur at an estimated frequency of 1 case per 6,000 to 10,000 live births in some countries in the developed world.

The incidence of Rubella and CRS throughout the world is directly related to the use of Rubella vaccines. For example, in the US, universal Rubella immunisation has eliminated Rubella and CRS. However, in much of Europe, Rubella immunization has been sub-optimal. Hence, Rubella and CRS are more common. Rubella and CRS are also common in developing countries.

Against this background, it is important to identify pregnant women at risk for a primary infection as early as possible and establish reliable diagnostic parameters for Rubella infection during pregnancy.

Since severe CRS is NOT the inevitable result of intrauterine Rubella virus infection, it is also necessary to define a diagnostic approach, with prognostic values regarding intrauterine damage, at a time when a decision can be made to terminate the pregnancy or carry the fetus to full term.

The purpose of this section is to review the key features and diagnosis of maternal and congenital Rubella infection, prevention, and treatment.

Section 1:

The Biology & Pathology of Rubella

In this section

Learning Objectives

After completing this section, you should be able to:

Indicate why Rubella infection is dangerous in pregnant women.

Indicate how Rubella is transmitted.

Name the major risk factors for Rubella infection.

Identify individuals at risk for severe consequences of Rubella infection.

Describe the symptoms and clinical course of the disease.

Describe ways of preventing infection.

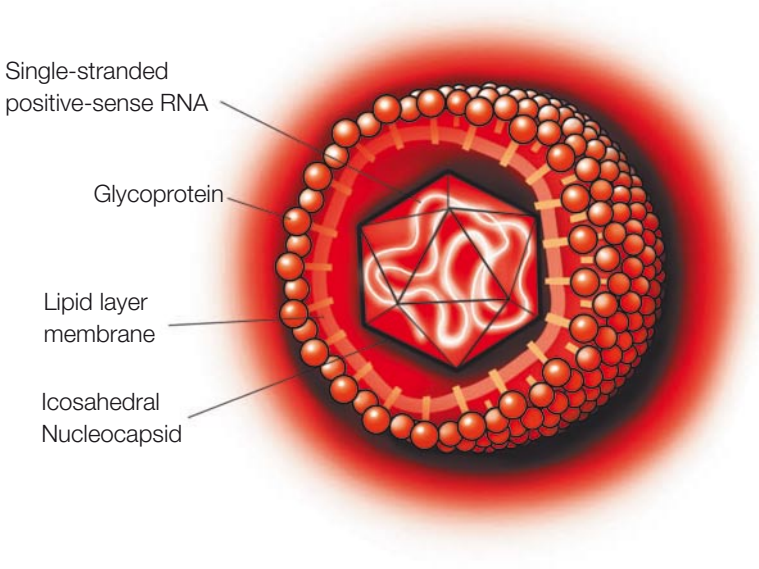
What is Rubella?

Rubella virus (RV), a Togavirus, is an enveloped virus with a single-stranded RNA genome.

Rubella virus is relatively unstable and rapidly inactivated.

Following respiratory transmission of Rubella virus, replication of the virus is thought to occur in the nasopharynx and regional lymph nodes. Viremia occurs 5 to 7 days after exposure with spread of the virus throughout the body and the chance of transplacental infection of the fetus.

Fetal damage happens through arrest in cell division as well as due to destruction of cells.



Rubella Virus

Epidemiology

In the pre-vaccine era, epidemics of Rubella occurred every 6 to 9 years. In the US Rubella epidemic of 1964–1965, 12.5 million cases of Rubella infections resulted in about 20,000 newborns with congenital Rubella syndrome (CRS).

United States

Vaccines were licensed in 1969 for use in the US, and no large epidemics have since occurred. Today, the only cases of CRS in the US occur in women who have contracted Rubella in other countries. Surveillance of Congenital Rubella Syndrome (CRS) has shown that the incidence parallels the decrease in Rubella cases, but has not vanished totally. An average of 5–6 cases have been reported annually since 1980.

Europe

Western Europe compares more favorably to the U.S. practice of universal childhood vaccination than do Eastern and Central Europe.

Japan

In Japan, nationwide epidemics of Rubella had occurred approximately every 5 years, namely in 1976, 1982, 1987 and 1992. For each epidemic, a minimum of 100 cases of CRS were reported.

Other nations

In much of the developing world, Rubella immunization has not been uniformly implemented. Therefore, Rubella and CRS continue to occur both in epidemics as well as in continued prevalence in some countries.

Biology & Pathology

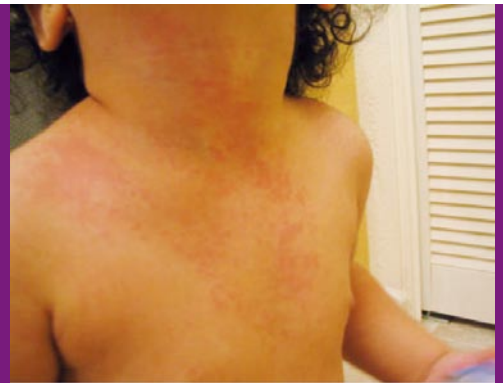
Primary/Acute Rubella Infection

Rubella virus enters the body via inhalation and infects cells of the respiratory tract. Rubella then spreads via the lymph nodes into the blood, where it induces an immune response resulting in lasting immunity.

Many rash illnesses may mimic Rubella infection, and up to 50% of Rubella infections may be subclinical (asymptomatic).

Immunity

IgG antibodies 10–15 IU/ml is indicative of immunity. In 95% of the cases, antibodies develop 10–28 days after vaccination. If a patient is subsequently infected with a typical Rubella virus strain, the patient is protected. However, in rare cases, wild strains of Rubella may cause a full blown reaction and subsequent infection.



Evidence of acute Rubella infection is determined by the presence of Rubella-specific IgM antibody, demonstration of a significant rise in IgG antibody from paired acute and convalescent sera, a positive viral culture for Rubella, or detection of Rubella virus by PCR.

Routes of Transmission

Mother to Unborn Baby

Intrauterine transmission of the virus from mother to developing fetus *in utero* during the first trimester presents greater risk for poor outcomes.

Person-to-Person Contact

Rubella is spread from person-to-person via airborne transmission of droplets shed from the respiratory secretions of infected persons.

Rubella may be transmitted by sub-clinical or asymptomatic cases.

Rubella is only moderately contagious and most so when the rash is erupting. However, the virus may be shed from 7 days before to 5–7 days or more after the onset of a rash.

Individuals at Risk

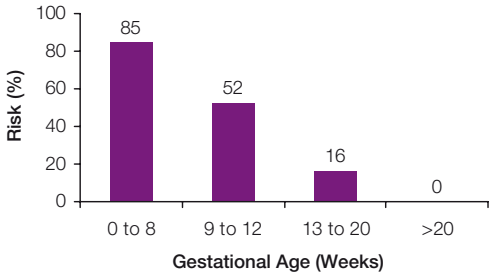
Risks of Acquiring Congenital Rubella

Estimated risks of acquiring congenital Rubella after infection in a pregnant woman vary considerably.

In temperate climates Rubella is a winter and spring disease, but some transmission and sporadic illness occurs year round in large urban areas.

In remote islands, large segments of the population may be susceptible. Introduction of the virus results in a major epidemic.

Estimated Risks of Congenital Rubella by Age

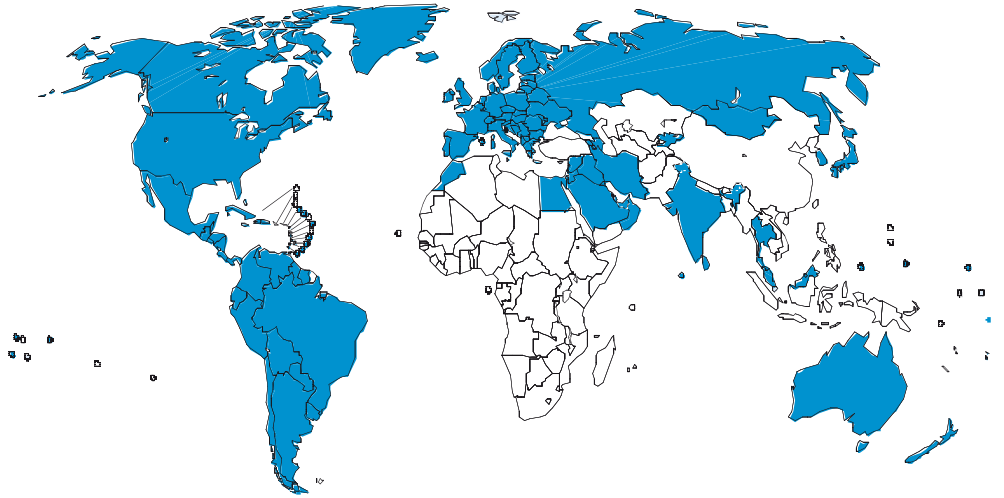


Risk of transmission to the fetus is greatest during the 0–8 weeks of gestation.

Incidence and Prevalence

Although the incidence of CRS has declined considerably in many countries as a consequence of Rubella vaccination, RV infections during pregnancy still occur at an estimated 1 case per 6000–10,000 live births in some industrialized countries where immunization programs are inadequate.

Countries using Rubella vaccines in their national immunization programs (Dec, 2003)



Source: WHO/UNICEF Joint Reporting Program, 2004

Rubella may re-emerge if vaccination programs cannot be adequately sustained.

In several countries, uptake of the combined Measles, Mumps, and Rubella (MMR) vaccine declined despite a consensus supporting use among most experts. The triple vaccine is the most effective way to control all three diseases.

Outbreaks of measles and mumps have already occurred in student and travelling communities. Although Rubella susceptibility rates are probably only about 2% overall for pregnant women, they are much higher among some minority ethnic groups which could be hit hard if Rubella outbreaks occur. Outbreaks have also occurred following decreased MMR usage. However, the incidence of outbreaks are very low overall.

Maternal & Congenital Symptoms

Although transmission of Rubella from mother to fetus may occur at any time during pregnancy, particularly severe sequelae have been reported due to infection during the first three months of pregnancy.

Maternal Symptoms

About half of Rubella cases remain asymptomatic. The primary symptom of Rubella virus infection is usually the appearance of fine, pink macules on the face. This rash typically spreads to the trunk and limbs and fades within 48 hours.

Other symptoms may include:

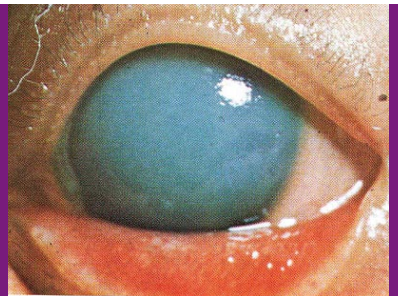
- Low-grade fever
- Lymphadenopathy
- Headache
- Fatigue
- Myalgia
- Sore throat

Congenital Symptoms

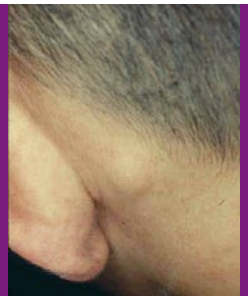
- Neurosensory deafness
- Blindness
- Congenital heart disease
- Microcephaly
- Hepatosplenomegaly

Neonatal Outcomes

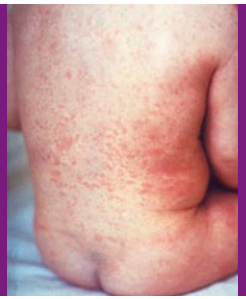
- Mental retardation
- Growth retardation
- Severe deafness, heart disease, and eye disease
- Death (10–20% in first year of life)



Severe congenital glaucoma due to Rubella. Dense corneal haze, enlarged corneal diameter, deep anterior chamber, and high ocular tension (Amer. J. Dis. Child 1965;110:416-427)



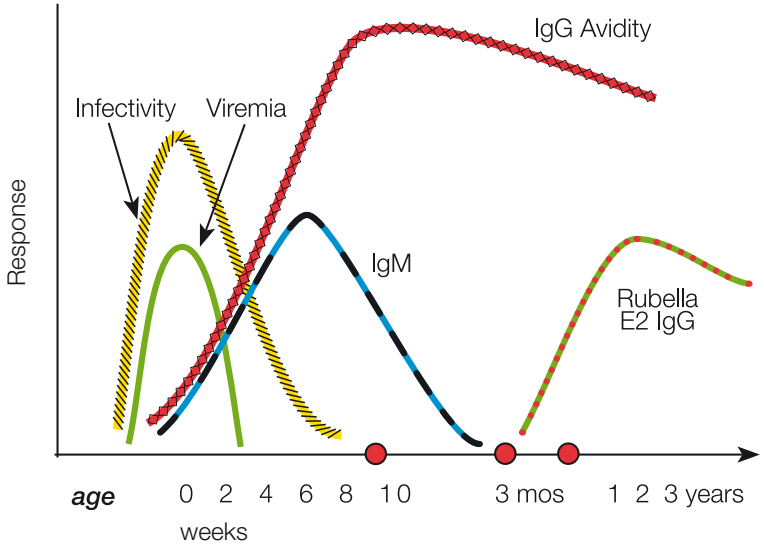
Posterior auricular lymph node enlargement



Pink macules

Rubella Serology

Serology Timeline



IgG

Detection of Rubella-specific IgG is used as a marker of Rubella vaccination or past infection.

IgM

IgM antibodies are detected in individuals with a recently acquired Rubella infection or soon after Rubella vaccination. However, Rubella IgM antibodies can persist for a year or longer. This test is normally ordered only when their has been exposure to Rubella infection or suspicion of Rubella infection.

IgG Avidity

Avidity maturation of Rubella-specific IgG occurs very quickly, within 2 months, and therefore is used in combination with other tests available only in research labs to determine the status of the Rubella infection.

Methods of Testing

Key diagnostic questions:

- Has this subject ever had Rubella? (detection)
- Is this a recent primary Rubella infection? (differentiation)
- Is fetal infection present?
- Is congenital Rubella infection present in this newborn?

Sources of samples	Maternal	Fetal
Non-blood		Amniotic fluid PCR
Blood	Maternal Blood antibody tests Virology tests	Cord blood for IgM antibody tests Fetal serum: IgM or IgA to demonstrate intrauterine infection
Other		Ultrasound detection of gross abnormalities

Types of serology tests	Maternal	Fetal
HIT The Hemagglutinin Inhibition Test is the reference assay for the determination of Rubella antibody titer. The ability of human anti-Rubella antibodies to inhibit agglutination of erythrocytes by the surface hemagglutination of Rubella forms the basis of the test. An antibody titer > 1:32 is thought to represent immunity to Rubella infection.	Positive test indicates vaccination or past infection	Positive test does not indicate infection
IgG Usually tested in maternal or fetal blood Limitations are that it is not conclusive of a current or active infection	Positive test indicates vaccination or past infection Should be done pre-pregnancy as a baseline to assess immunity to Rubella	Positive test does not indicate infection
IgM Marker for primary Rubella infection or reinfection Indirect enzyme immunoassay may lead to non-specific results False positives may occur due to cross-reactivity and rheumatoid factor; parvovirus; and mononucleosis	Although normally detectable for only 1–2 months may persist for up to 12 months after initial infection Can be produced as a result of poly-clonal stimulation of Rubella specific B-lymphocytes by EBV virus Recommend use with virology tests	A Rubella IgM-positive result alone does not accurately predict the risk of fetal infection; should be followed by a viral PCR Rheumatoid factor, parvovirus IgM, and heterophile tests should be done if false-positive is suspected
IgG avidity Measures the functional binding affinity of the IgG class of antibody in response to infection Helps distinguish between primary and non-primary infection.	Acute Phase Reactant (< 2–3 months): Low avidity *Low avidity Index: 1–30%* Chronic Phase Reactant (> 4 months): High Avidity *High avidity Index: > 60%*	Not tested
E2 IgG This test measures the levels of human anti-Rubella IgG antibody against the E2 protein of Rubella virus using an Immunoblot assay. Detection of E2 IgG antibodies is used to exclude acute infection.	Detection of E2 IgG antibodies is used to exclude acute infection.	Detection of E2 IgG antibodies is used to exclude acute infection.
SP15 IgG This test measures the levels of human anti-Rubella IgG antibody directed against E1 peptide comprising amino acids 208–239. This test is used during prenatal and infant diagnosis to assess the risk of development of CRS.	Not tested	Infants with CRS have lower levels of SP15 IgG than asymptomatic RV-infected infants

Source: Pustowoit and Liebert, Intervirology, 1998

Quiz Questions

1. Rubella Virus results in particularly severe sequelae in the congenitally-infected fetus when acquired for the very first time by the mother in the:

A. First trimester
B. Second trimester
C. Third trimester

2. Is it possible that a mother with an acute infection may be asymptomatic?

A. No
B. Yes

3. The following is not seen in congenital Rubella:

A. Blindness
B. Missing fingers
C. Deafness

4. IgG antibodies, if detected in the fetus:

A. Are inconclusive
B. Require re-testing
C. Confirm an infection

5. IgG avidity tests in the fetus are tested in the:

A. First trimester
B. Third trimester
C. Not tested

1. A
2. B
3. B
4. A
5. C

Section 2:

Case Studies

In this section

Learning Objectives

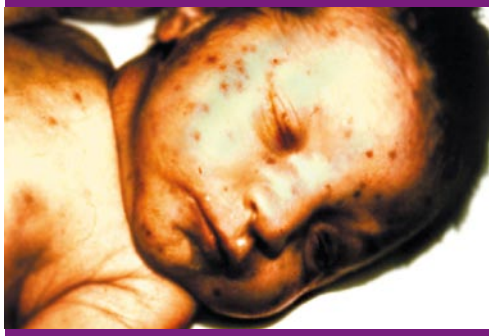
After completing this section, you should be able to:

Identify and describe the different types of tests employed in the diagnosis of Rubella infection in pregnant women.

Recognize the utility and limitations of the diagnostic algorithm for Rubella in pregnant women.

Requirements or practice of serologic screening of pregnant women for Rubella in different countries.

Laboratory tests for the diagnosis of Rubella infection in pregnant women (include serology, virology and PCR).



Case Study 1:

Early Rubella Primary Infection

This patient was a pregnant woman in the 11th week of her first pregnancy.

She was 29 years old and had not received any Rubella immunization nor presented with any clinical symptoms.

Results of serological tests as result of obligatory testing in preparation to a pregnancy were as follows:

RV titer (HIT)	IgG	RV IgM (direct)	RV IgM #2 (μ-capture assay)
Positive (1:16)	10 IU/mL Intermediate reactive	–	Borderline +

Need for Repeated Testing

To verify a Rubella primary infection, it was necessary to collect an additional serum sample from this woman. The low Rubella IgG antibody content and the low HIT result of the first test battery reflected a possible early Rubella infection. To confirm findings similar to this, it is obligatory to repeat the IgM and IgG testing after 10–14 days.

Results of the second round of tests:

RV titer (HIT)	IgG	RV E2-IgG	IgG Avidity
Positive (1:256)	55 IU/mL Intermediate reactive	–	Low (25%)

Second Results

In this testing, Rubella IgM antibodies were again borderline and the IgG content increased to 55 IU/ml in ELISA and 1:256 in HIT. As such, the Rubella immunoblot and the Rubella IgG avidity testing were useful in determining a primary infection.

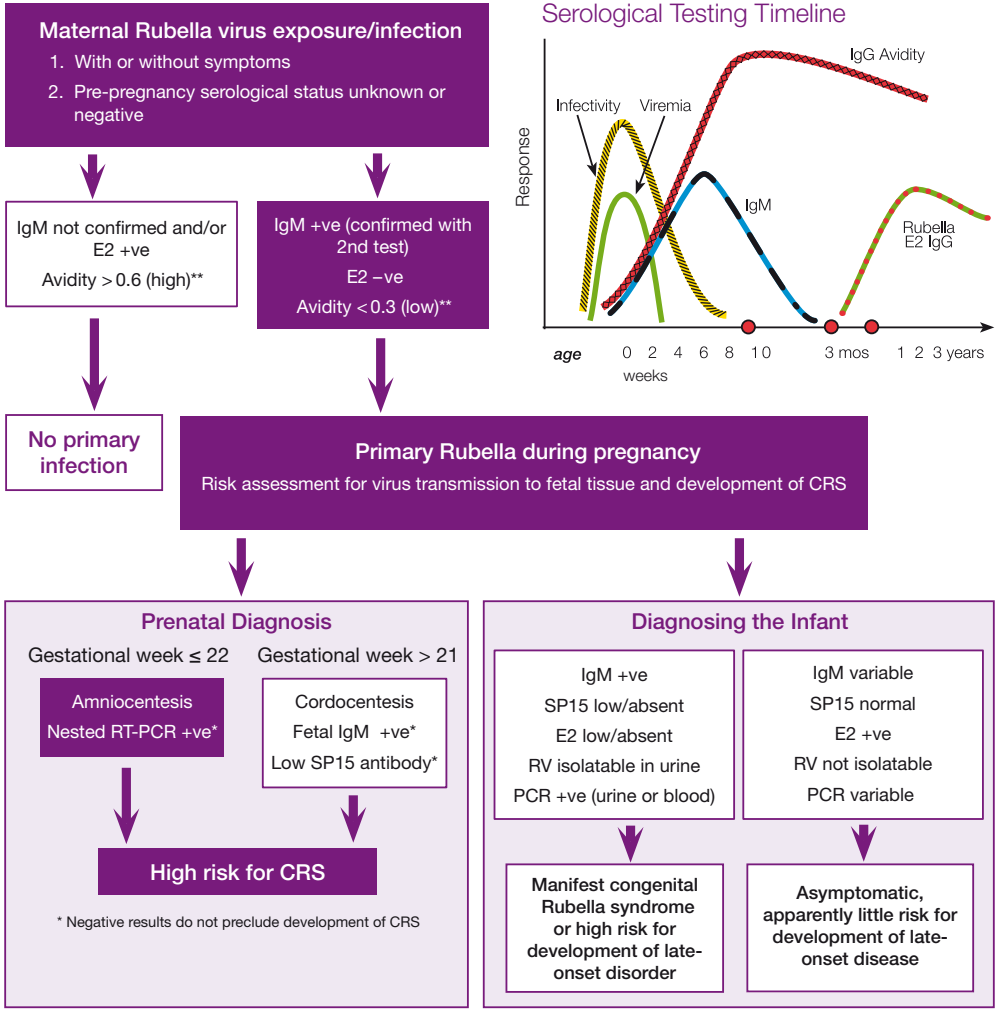
The Rubella immunoblot revealed no E2-IgG-conformation antibodies, and the avidity testing revealed low avidity of Rubella antibodies (25%).

Diagnosis & Prognosis

Rubella primary infection in the first trimester or during the time of conception, which indicates high risk for an infected fetus.

Case Study 1:

Protocol for Management



** To differentiate primary and non-primary infection, IgG Avidity and E2 IgG are performed at the same time. E2 IgG, IgG Avidity, and PCR tests available only in research labs

AV = Avidity index; SP15 = antibody reactive with SP15 peptide in EIA; E2 = envelope protein as detected in Immunoblot Assay; +ve = positive, detectable; –ve = negative or undetectable

Source: Pustowoit and Liebert, Intervirology (1998)

Case Study 2:

Rubella Reinfection

A 30 year old patient in the 4th month of her first pregnancy was investigated during the preparation stage for pregnancy.

She was vaccinated 10 years ago.

The titre in HIT was 1:32 and Rubella IgG ELISA are tested 25 IU/ml. Two different Rubella IgM tests were done with a weak positive result:

RV titer (HIT)	IgG	RV IgM #1	RV IgM #2
1:32 (1:32 corresponds to borderline intermed-hi	25 IU/mL Borderline intermediate high	Weak +	Weak +

The next step is to exclude a primary Rubella infection.

Additionally, Rubella immunoblot and Rubella IgG avidity testing were done. E2-IgG-confirmation antibodies were detected, and the avidity index was 89%, which reflected the presence of high avidity antibodies.

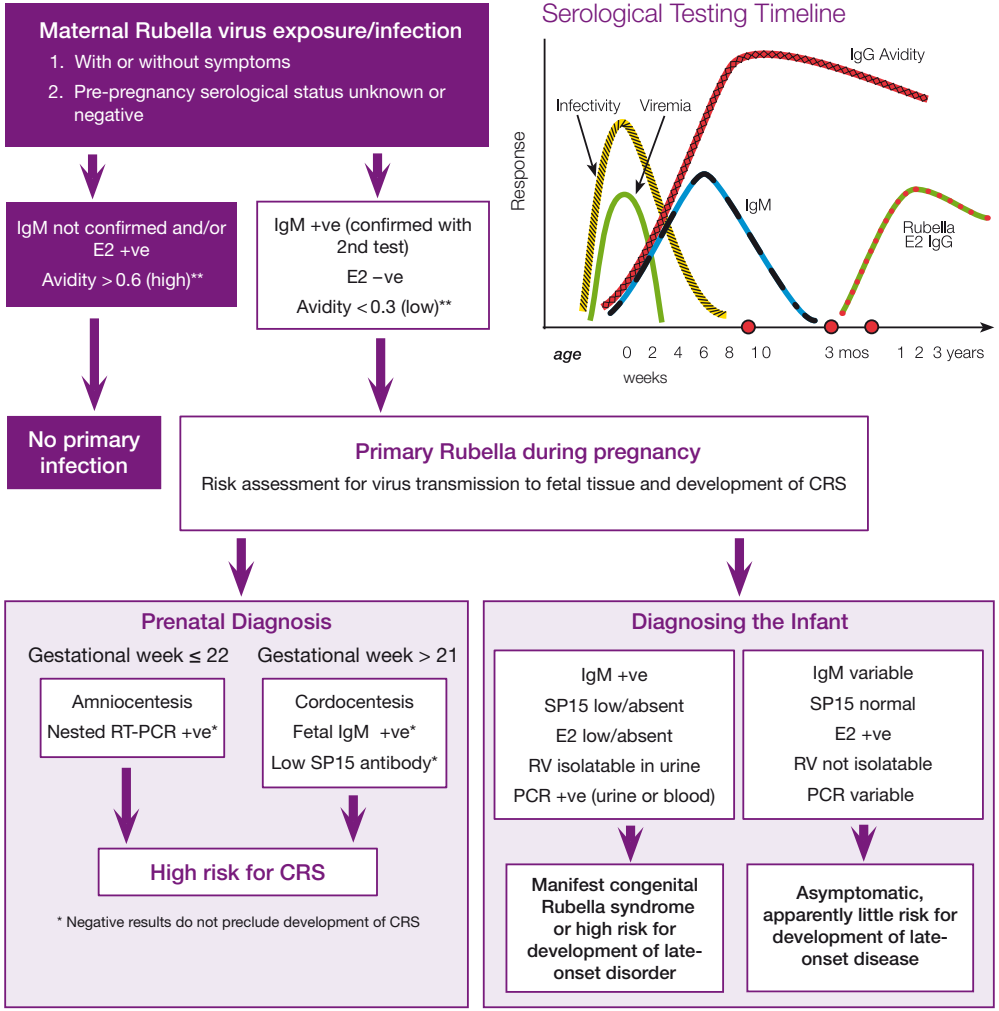
RV immunoblot E2-IgG	IgG Avidity
+	High (89%)

Diagnosis

A Rubella primary infection was ruled out. The Rubella IgM antibodies underlined a Rubella re-infection.

Case Study 2:

Protocol for Management



** To differentiate primary and non-primary infection, IgG Avidity and E2 IgG are performed at the same time. E2 IgG, IgG Avidity, and PCR tests available only in research labs

AV = Avidity index; SP15 = antibody reactive with SP15 peptide in EIA; E2 = envelope protein as detected in Immunoblot Assay; +ve = positive, detectable; –ve = negative or undetectable

Case Study 3:

Congenital Rubella

The infant's family came to the US in February, 2004, from a refugee encampment in Ivory Coast, Africa. At that time, the mother did not know she was pregnant.

On March 1, 2004, the mother received the MMR vaccine at a local health department refugee health screening program.

On March 26, 2004, the mother was found to be pregnant, and one month later, the mother was determined to be Rubella-immune on the basis of a screening antibody assay.

On November 4, 2004, the mother gave birth to a female infant with a left eye cataract.

Ten weeks later, the baby was found to have microcephaly, patent ductus arteriosus, bilateral hearing impairment, hepatosplenomegaly, and failure to thrive. CRS was suspected.

IgM	Urine	Nasopharyngeal
+	+	+

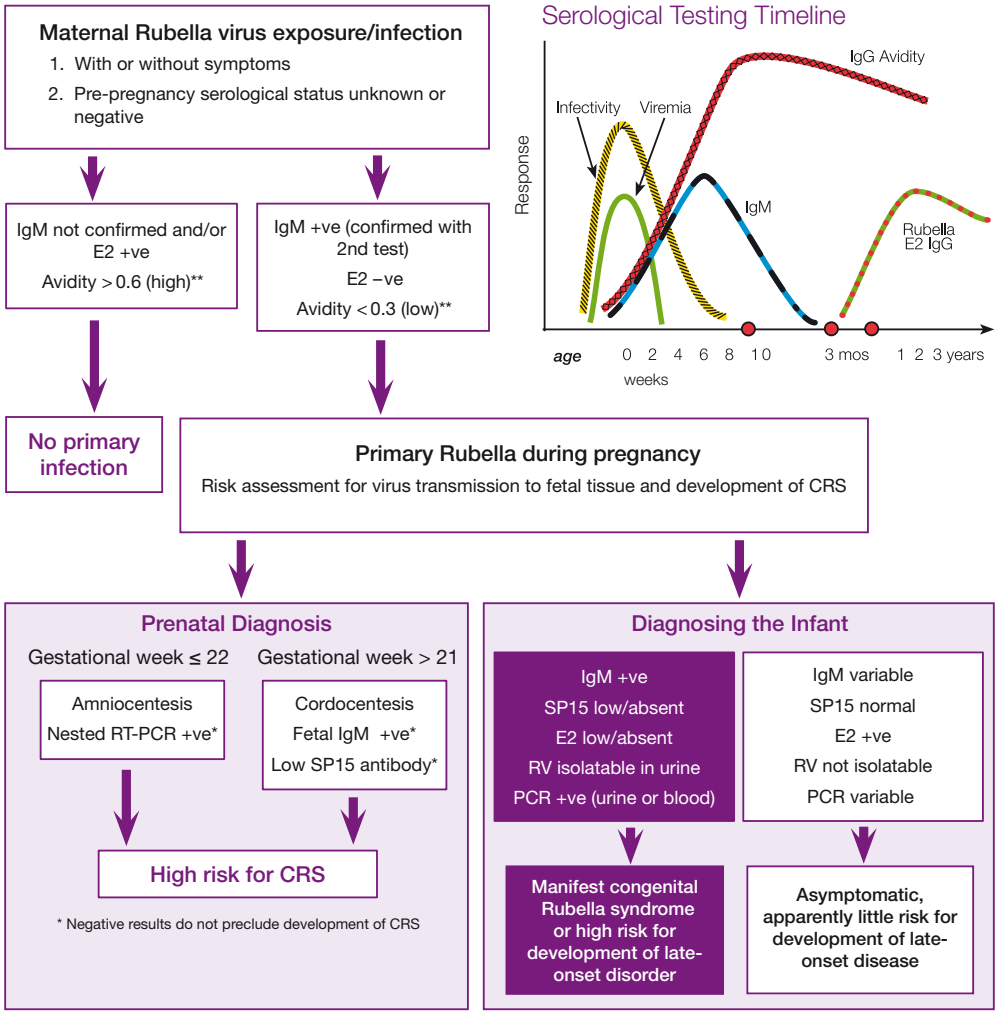
Diagnosis

The diagnosis was confirmed with a positive Rubella IgM and positive cultures from urine and nasopharyngeal specimens.

The virus was determined to be wild-type Rubella virus and not a vaccine virus by genetic sequence analysis.

Case Study 3:

Protocol for Management



** To differentiate primary and non-primary infection, IgG Avidity and E2 IgG are performed at the same time. E2 IgG, IgG Avidity, and PCR tests available only in research labs

AV = Avidity index; SP15 = antibody reactive with SP15 peptide in EIA; E2 = envelope protein as detected in Immunoblot Assay; +ve = positive, detectable; –ve = negative or undetectable

Prevention & Treatment

Prevention

The only way to prevent Rubella infection is universal, active immunization programs using live, attenuated virus vaccines. It is instrumental to implement universal Rubella immunization of children and older persons who have not had Rubella or in Rubella antibody testing are found to be non-immune.

Today, in most countries, Rubella vaccines are given as part of the MMR vaccine. The first administration is at 12–18 months, with a second dose at 36 months (based on WHO recommendations). In some countries, parents choose to have the second dose administered at variable times beyond 1 month following the first dose.

Vaccination Before Pregnancy or for Women of Child-Bearing Age

During their first visit with a gynecologist or obstetrician, women should be tested with a Rubella IgG test to determine their immune status.

At this time, Rubella IgM studies should not be performed because false positive tests are common, and they can lead to patient anxiety and unnecessary measures.

Follow up in Cases of Known Exposure

In cases of seronegative women contacting an infected person during pregnancy, it is important to investigate the pregnant woman after 3 weeks using a Rubella IgM-test. Tests administered before 3 weeks are susceptible to false-positives.

Treatment of Newborns With Rubella

Most treatments focus on managing complications, especially mental retardation, blindness, congenital heart disease, and deafness. Congenital heart defects can be surgically corrected, cataracts can be removed, and deaf children can be enrolled in early education programs. However, prognoses for these infants vary and are often poor.

Fetal Intervention

At the present time, the only intervention available for congenital Rubella infection is termination of the pregnancy. Careful use of prenatal maternal and fetal diagnostic tests should reduce the likelihood that termination of pregnancies will be chosen when there is no evidence of fetal damage.

The only way to prevent Rubella infection is universal, active immunization programs using live, attenuated virus vaccines.

Quiz Questions

1. What preliminary Rubella virus test should be done during the first pelvic exam by a gynecologist?

A. IgG Avidity
B. IgM
C. IgG

2. Rubella virus vaccination may be done individually or via combination MMR.

A. False
B. True

3. Which of the following does not exclude a primary Rubella infection?

A. E2-IgG Positive
B. E2-IgG Negative
C. Highly avidity IgG

4. Newborns with Rubella infections have positive IgM levels.

A. True
B. False

5. The finding of a negative Rubella IgG antibody screening test in a non-pregnant patient requires that you:

A. Continue observation
B. Do an IgM test
C. Vaccinate the patient

1. C
2. B
3. B
4. A
5. C

References

Best JM, Castillo-Solorzano C, Spika JS, Icenogle J, Glasser JW, Gay NJ, Andrus J, Arvin AM. Reducing the global burden of congenital Rubella syndrome: report of the World Health Organization Steering Committee On Research Related To Measles and Rubella Vaccines and Vaccination, June 2004. J Infect Dis. 2005 Dec 1;192(11):1890-7

Centers for Disease Control and Prevention. Control and prevention of Rubella: evaluation and management of suspected outbreaks, Rubella in pregnant women, and surveillance for congenital Rubella syndrome. MMWR 2001;50(No. RR-12) 1-24

Pustowoit, B. and Liebert, U.G. (1998). Predictive Value of Serological Tests in Rubella Virus Infection during Pregnancy. Intervirology 41:170-177.

Rubella seminar. The Lancet. Vol 363. J E Banatvala, D W G Brown 2004; 1127-37.

About the Author

Prof. Barbara Pustowoit

Barbara Pustowoit is a Professor of the University of Leipzig's Institute of Virology. Her recent professional engagements include Head of the National Rubella Virus Reference Laboratory of the former GDR and Chief of the *ad hoc* Commission "Rubella" with the German Assoc. for Prevention of Virus Infections. Prof. Pustowoit has authored and contributed to over three dozen books, peer-reviewed publications, and policy guidelines on infectious disease and genomics in multiple languages, and has been awarded several patents for her research in genomics/proteomics. She received her degrees in microbiology and chemistry from the Universities of Leipzig and Moscow, respectively.

She maintains affiliation with the Association for Microbiology, Association for Virology, European group for rapid virus diagnostic, German Society for Virology, and the Association for protection of viral infections (Germany).

Glossary

AC/HS	A differential agglutination test which compares human anti-Toxo IgG titers obtained with formalin-fixed tachyzoites (HS antigen) with those obtained with acetone- or methanol-fixed tachyzoites (AC antigen). This test is very useful in helping differentiate between acute and chronic infections.
Acute	Early stage of a primary infection, usually < 4 months post-infection.
Amniocentesis	Procedure performed by a physician to withdraw amniotic fluid surrounding the fetus from a pregnant woman for analysis.
Amniotic fluid	Clear, slightly yellow liquid contained within the amniotic sac which surrounds the fetus.
Antibody	A Y-shaped protein molecule (immunoglobulin) in serum or body fluid that either neutralizes an antigen or tags it for attack by other cells or chemicals; acts by uniting with and firmly binding to an antigen. The prefix “anti-” followed by initials of an infectious agent (virus, parasite, etc.) refers to a specific antibody against the infectious agent.
Asymptomatic	Symptoms of the infection are not present.
Avidity	Measurement of the functional binding affinity of an immunoglobulin.
Axillary	Cavity beneath the junction of the arm to the body, also known as the armpit.
Benign	Refers to a condition, tumor, or growth which is non-cancerous.
Biopsy	Procedure performed by a physician to remove a sample of body tissue for testing.
Cerebral Palsy	Group of conditions that affect control of movement and posture. Maternal CMV, Toxo, and Rubella infections transmitted to the fetus may cause fetal brain damage resulting in this condition.
Chorioretinitis	Inflammation of the choroid (vascular layer behind the retina) and retina of the eye.
CMV (Cytomegalovirus)	A beta-herpesvirus which establishes latency in the host upon infection.

CMV IgG	Immunoglobulin class G antibodies directed against CMV.
CMV IgG Avidity	Describes the functional binding affinity of an immunoglobulin class G antibody against CMV.
CMV IgM	Immunoglobulin class M antibodies directed against CMV.
Congenital Rubella Syndrome (CRS)	A collection of symptoms present in the newborn infant consistent with intrauterine acquisition of Rubella infection.
Congenital	Medical condition present at birth due to genetic factors, intrauterine transmission of maternal infection (e.g., CMV, *Toxoplasma*, Rubella), or unknown factors.
Cord blood	Human blood from the placenta and umbilical cord.
Cyst	Fluid filled sac containing a membrane located anywhere in the body.
Desiccation	Process or state of extreme dryness.
DNA (Deoxyribonucleic acid)	The coded genetic material in the nucleus of most cells that controls heredity; automatically controls the formation of RNA, which spreads throughout the cell and controls the formation of specific proteins. The genomes of CMV and *Toxoplasma gondii* contain DNA.
E2 IgG	Human IgG antibodies against the E2 envelope protein of Rubella virus. These antibodies appear later during acute Rubella infection and can be measured by a non-reducing immunoblot assay.
ELISA (Enzyme Linked ImmunoSorbent Assay)	Biochemical technique used to detect antibody or antigen in a patient sample using two antibodies.
Endothelial cells	Cells which line the entire circulatory system.
Epidemic	Sudden rise in new cases of a disease in the human population.
Exanthem	A widespread skin eruption or rash accompanying a viral infection.
Exanthematous	Condition characterized by a widespread skin eruption or rash.
Exposure	Presentation of an infectious disease causing agent to a non-immune individual.
Fundus oculi	The concave interior of the eye including the retina, choroid, sclera, optic disk, and blood vessels as viewed by an ophthalmoscope.
Ganciclovir (GCV)	An antiviral drug used to treat symptoms of CMV infection. It is a synthetic analogue of 2'-deoxy-guanosine which causes chain termination of replicating viral DNA.

Gestation	The carrying of an embryo or fetus in the uterus of a pregnant female.
Hemagglutinin Inhibition Test	This test can only be performed with a virus which contains a surface protein that can agglutinate red blood cells (RBCs) and is used to measure antibody titers against said virus. In the first step of the test, serial dilutions of the patient sample are mixed with virus. After incubation, RBCs are added followed by further incubation. If antibodies are present against the virus, the antibodies bind to the virus and prevent the agglutination of the RBCs by the virus. The hemagglutination inhibition titer (HI) of the sample is the highest dilution at which hemagglutination is prevented. This test can be used to measure Rubella antibody titers.
Hepatic transaminases	Refers to the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which are released into the serum during hepatocellular necrosis, i.e. liver damage.
Hepatosplenomegaly	Simultaneous enlargement of both the liver and spleen.
Herpesvirus	Group of viruses that can establish latency in the host. Viral DNA persists in the host for the lifetime of the individual.
Hyperbilirubinemia	Condition associated with elevated levels of bilirubin in the blood serum.
Hyperechogenic	Amplitude of the echoes during ultrasonic evaluation are greater or brighter than normally seen for the region of the body under examination. May indicate a disease state is present.
Hyperimmuno-globulin	Elevated levels of immunoglobulins.
IgG	Immunoglobulin class G antibody provides the majority of humoral immunity in response to infection.
IgM	Immunoglobulin class M antibody appears early during infection and can also reappear during viral reactivation or secondary viral infections.
Immune	A state of protection afforded against infection as the result of the presence of antibodies in the body's circulatory system.
Immunization	Introduction of either an attenuated infectious agent or parts thereof in order to develop protective immunity against disease.
Immunoblot	A technique for analyzing proteins or antibodies using antigen-antibody specific reactions on a solid phase, such as in a Western blot or Dot blot.

Immunodeficient	Lacking immunity and therefore susceptible to infection.
Immunosuppression	Reduction in the activation or efficacy of the immune system.
Incidence	The number of new episodes of illness arising in a population over an estimated period.
Inguinal hernia	Protrusion of part of the intestine through the lower abdominal wall.
Intrapartum transmission of infection	Acquisition of maternal infection by the fetus during labor.
Intrauterine transmission of infection	Acquisition of maternal infection by the fetus within the uterus.
Jaundice	A syndrome characterized by increased levels and deposits of bile pigment in the skin, giving the individual a yellowish skin color and may include yellowing of the whites of the eyes; usually caused by liver changes.
Kitty litter	Absorbent material placed in a container and used to collect cat urine and feces.
Latency	Dormant state of an infectious agent within a host that later can produce an active infection.
Leucovorin calcium	Also known as folinic acid, is prescribed to patients undergoing pyrimethamine therapy to protect the bone marrow from the toxic effects of pyrimethamine.
Lymph nodes	Small (0.5 – 2 cm) bean-shaped components of the lymphatic system filled with lymphocytes that destroy infectious agents.
Lymphadenopathy	Swelling of the lymph nodes and a symptom of many diseases.
Lymphocyte	White blood cells responsible for humoral (B cells) and cellular immunity (T and NK cells).
Lytic infection	Infection of host cells by an infectious agent resulting in lysis of the host cell and release of additional infectious agent.
Macrophages	Differentiated from monocytes, these cells engulf and ingest (phagocytize) cellular debris and pathogens present in tissues.
Macules	Flat dermatological lesion noted by a change in color.
Malaise	A general feeling of being unwell; feeling may be accompanied by identifiable physical discomfort and may indicate the presence of disease.

Marker	An antigen or antibody used to indicate the status of disease or recovery.
Meningoencephalitis	Inflammation of the brain and surrounding membrane.
MMR – Measles, Mumps, Rubella	The Measles, Mumps, Rubella vaccine is normally administered in two doses, at ages 12–15 months and 4–6 years of age (CDC Guidelines).
Monocytes	Produced in the bone marrow these cells engulf and ingest (phagocytize) cellular debris and pathogens present in blood. They are progenitor cells for macrophages which perform the same activity in tissues.
Mononucleosis	Also known as mono or kissing disease caused by Epstein-Barr (EBV) or CMV infection of lymphocytes, resulting in elevated white cell counts (monocytes and lymphocytes).
Morbidity	The state of being diseased.
Mortality	The state of being deceased.
Mucosal	Mucous membranes line various body cavities and internal organs. These cells are involved in absorption and secretion (mucus).
Myalgia	Pain in the muscles.
Nasopharynx	Region of the upper throat that lies behind the nose.
Neonatal	A newborn child usually less than 1 month old.
Neutropenia	Abnormally low number of neutrophil granulocytes which make up 50–70% of the white cell count. Neutrophils destroy bacteria in the blood.
Nonprimary infection	A secondary infection caused by reactivation of a latent infection or reinfection of the host.
Oocyst	Spore phase of *Toxoplasma gondii* formed inside the intestines of the cat.
Optic atrophy	Loss of nerve fibers from the optic nerve of the eye.
Parasite	An infectious agent dependent on another organism or cell for replication and survival.
PCR	Polymerase Chain Reaction is a biochemical technique which can specifically amplify a target DNA molecule several thousand fold using oligonucleotide primers and a thermostable DNA polymerase.
Peripectoral	Area surrounding the chest.

Petechiae	Pinpoint-sized red dots under the skin caused by leakage of blood from capillaries into the skin. Thrombocytopenia (low platelet count) is a common cause of this condition.
Plasma	The straw-colored liquid component of blood.
Prenatal	Period of time before birth.
Prevalence (of a disease)	The percentage of a population that is affected with a particular disease at a given time.
Primary host	A host in which the parasite grows to a mature state.
Primary infection	First presentation of an infectious agent to a non-immune host.
Purpura	Large red areas of bleeding into the skin which later turn purple and brownish-yellow. This condition can be caused by thrombocytopenia.
Pyrimethamine	A substituted phenylpyrimidine anti-malarial drug particularly effective against *T. gondii* in infected individuals when co-prescribed with sulfadiazine.
Reinfection	A second infection by the same infectious agent.
Replication	The process whereby an organism, cell, virus, parasite, or the genome contained therein is duplicated.
RNA (Ribonucleic acid)	A substance formed in the cell nucleus, under the control of DNA; transfers genetic information from DNA into the cytoplasm of the cell for the synthesis of proteins. The genomes of some viruses, for example Rubella, utilize single strand RNA as the genetic material.
Rubella	Commonly known as German measles, caused by infection with Rubella virus.
Rubella IgG	Immunoglobulin class G antibodies directed against Rubella.
Rubella IgG Avidity	Describes the functional binding affinity of an immunoglobulin class G antibody against Rubella.
Rubella IgM	Immunoglobulin class M antibodies directed against Rubella.
Sabin-Feldman Dye Test	This test is used to detect human anti-*T. gondii* antibodies and is based on the observation that when living tachyzoites are incubated with normal serum, they become swollen and stain blue when methylene blue is added to the suspension. Living parasites exposed to antibody-containing serum, under the same conditions, appear thin, distorted, and are not stained when the dye is added.

Screening	Testing an asymptomatic population with a diagnostic test.
Secondary host	A host which harbors the parasite for a transition period.
Sensorineural hearing loss	An irreversible hearing loss caused by damage to the cochlear nerve and can lead to total deafness.
Sequelae	An illness or condition that follows as a consequence of another disease (singular form: sequela).
Seroconversion	An immune response that is characterized by a conversion from the absence of a specific antibody to the presence of that specific antibody in a patient or the disappearance of an antigen followed by the appearance of its corresponding antibody.
Serological	Pertaining to antigen-antibody reactions *in vitro*.
Serology	Diagnostic test to detect antibodies in blood serum.
Seronegative	Blood serum showing a negative result to a particular test.
Seropositive	Blood serum showing a positive result to a particular test.
Serum	Blood plasma after removal of clotting factors (plural form: sera).
SP15 IgG	This test measures the levels of human anti-Rubella IgG antibody directed against the epitopes contained in amino acids 208 – 239 of the Rubella E1 envelope protein.
Spiramycin	A macrolide antibiotic used to treat pregnant females infected with *T. gondii* early in gestation to attenuate intrauterine transmission of the parasite.
Subclinical	Clinical symptoms of disease are not visible.
Sulfadiazine	A sulphonamide antibiotic used in combination with pyrimethamine to treat *T. gondii* infection.
Supraclavicular	The area of the body located right above the collarbone.
Syndrome	A set or collection of medical symptoms and signs that occur together.
T. gondii	An obligate intracellular protozoan parasite that can cause devasting disease in the fetus and newborn infant.
Tachyzoite	The crescent-shaped, rapidly multiplying asexual stage of *T. gondii*.
Togavirus	A family of viruses of which Rubella virus belongs.
Toxo IgG	Immunoglobulin class G antibodies directed against *T. gondii*.

Toxo IgG Avidity	Describes the functional binding affinity of an immunoglobulin class G antibody against *T. gondii*.
Toxo IgM	Immunoglobulin class M antibodies directed against *T. gondii*.
Toxoplasmosis	Disease caused by infection with *T. gondii*.
Transplacental	Transmission through or across the placenta.
Ubiquitous	Existing everywhere, widespread.
Vaccine	Biological preparation consisting of an adjuvant and an attenuated infectious agent or parts thereof in order to develop protective immunity against disease.
Ventriculomegaly	Enlargement of the ventricules of the brain.
Viral culture	Laboratory technique to demonstrate the presence of infectious virus in tissue culture.
Viremia	The presence of virus in human blood.
Virology	The study of viruses and their interaction with susceptible hosts.
Virus	An infectious agent usually consisting of genetic material (DNA or RNA) packaged in a protein coat (capsid) which requires infection of a suitable host cell in order to replicate itself.
White blood cells	Cells in the blood produced by the bone marrow responsible for defending the body against invading pathogens and foreign materials.

Notes

Notes