Congenital Viral Infections

An Overview

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Congenital, Perinatal, and Neonatal Viral Infections

Intrauterine Viral Infections

Rubella
Cytomegalovirus (CMV)
Parvovirus B19
Varicella-Zoster (VZV)
Enteroviruses
HIV
HTLV-1
Hepatitis C
Hepatitis B
Lassa Fever
Japanese Encephalitis

Perinatal and Neonatal Infections

Human Herpes Simplex
VZV
Enteroviruses
HIV
Hepatitis B
Hepatitis C
HTLV-1

Rubella

History

1881 Rubella accepted as a distinct disease

1941 Associated with congenital disease (Gregg)

1961 Rubella virus first isolated

1967 Serological tests available

1969 Rubella vaccines available

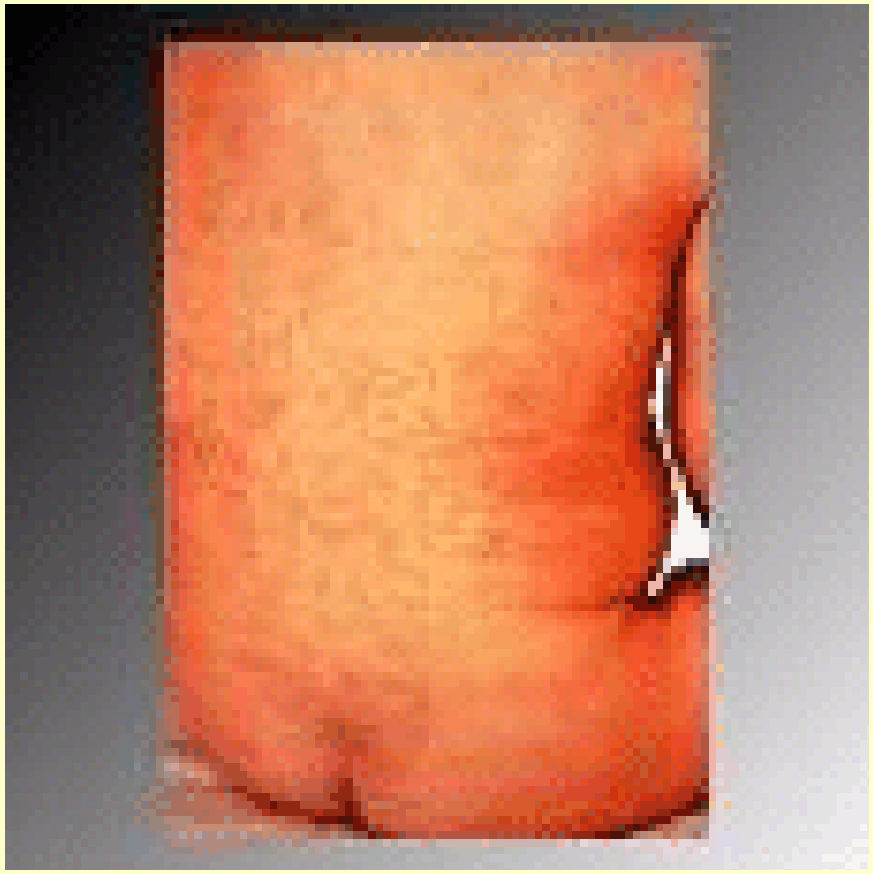
Characteristics of Rubella

- RNA enveloped virus, member of the togavirus family
- Spread by respiratory droplets.
- In the prevaccination era, 80% of women were already infected by childbearing age.

Clinical Features

- maculopapular rash
- lymphadenopathy
- fever
- arthropathy (up to 60% of cases)

Rash of Rubella



Risks of rubella infection during pregnancy

Preconception	minimal risk
0-12 weeks	100% risk of fetus being congenitally infected resulting in major congenital abnormalities. Spontaneous abortion occurs in 20% of cases.
13-16 weeks	deafness and retinopathy 15%
after 16 weeks	normal development, slight risk of deafness and retinopathy

Congenital Rubella Syndrome

Classical triad consists of cataracts, heart defects, and sensorineural deafness. Many other abnormalities had been described and these are divided into transient, permanent and developmental.

Transient	low birth weight, hepatosplenomegaly, thrombocytopenic purpura bone lesions, meningoencephalitis, hepatitis, haemolytic anemia pneumonitis, lymphadenopathy
Permanent	Sensorineural deafness, Heart Defects (peripheral pulmonary stenosis, pulmonary valvular stenosis, patent ductus arteriosus, ventricular septal defect) Eye Defects (retinopathy, cataract, microopthalmia, glaucoma, severe myopia) Other Defects (microcephaly, diabetes mellitis, thyroid disorders, dermatoglyptic abnormalities
Developmental	Sensorineural deafness, Mental retardation, Diabetes Mellitus, thyroid disorder

Outcome

- 1/3 rd will lead normal independent lives
- 1/3 rd will live with parents
- 1/3rd will be institutionalised

The only effective way to prevent CRS is to terminate the pregnancy

Prevention (1)

Antenatal screening

- All pregnant women attending antenatal clinics are tested for immune status against rubella.
- Non-immune women are offered rubella vaccination in the immediate post partum period.

Prevention (2)

- Since 1968, a highly effective live attenuated vaccine has been available with 95% efficacy
- Universal vaccination is now offered to all infants as part of the MMR regimen in the USA, UK and a number of other countries.
- Some countries such as the Czech Republic continue to selectively vaccinate schoolgirls before they reach childbearing age.
- Both universal and selective vaccination policies will work provided that the coverage is high enough.

Laboratory Diagnosis

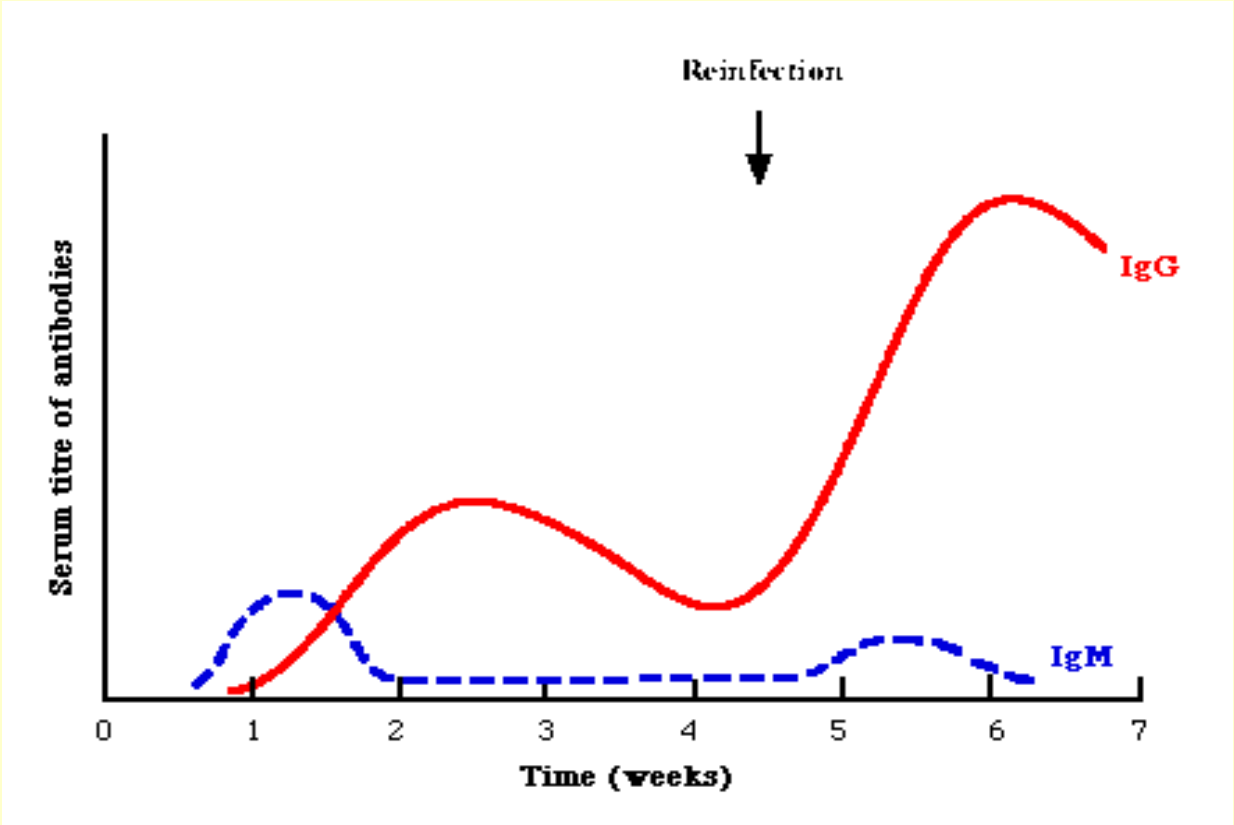
Diagnosis of acute infection

- Rising titres of antibody (mainly IgG) - HAI, EIA
- Presence of rubella-specific IgM - EIA

Immune Status Screen

- HAI is too insensitive for immune status screening
- SRH, EIA and latex agglutination are routinely used
- 15 IU/ml is regarded as the cut-off for immunity

Typical Serological Events following acute rubella infection



Note that in reinfection, IgM is usually absent or only present transiently at a low level

Cytomegalovirus

- member of the herpesvirus
- primary infection usually asymptomatic. Virus then becomes latent and is reactivated from time to time.
- transmitted by infected saliva, breast milk, sexually and through infected blood
- 60% of the population eventually become infected. In some developing countries, the figure is up to 95%.

Congenital Infection

- Defined as the isolation of CMV from the saliva or urine within 3 weeks of birth.
- Commonest congenital viral infection, affects 0.3 - 1% of all live births. The second most common cause of mental handicap after Down's syndrome and is responsible for more cases of congenital damage than rubella.
- Transmission to the fetus may occur following primary or recurrent CMV infection. 40% chance of transmission to the fetus following a primary infection.
- May be transmitted to the fetus during all stages of pregnancy.
- No evidence of teratogenecity, damage to the fetus results from destruction of target cells once they are formed.

Cytomegalic Inclusion Disease

- CNS abnormalities - microcephaly, mental retardation, spasticity, epilepsy, periventricular calcification.
- Eye - choroidoretinitis and optic atrophy
- Ear - sensorineural deafness
- Liver - hepatosplenomegaly and jaundice which is due to hepatitis.
- Lung - pneumonitis
- Heart - myocarditis
- Thrombocytopenic purpura, Haemolytic anaemia
- Late sequelae in individuals asymptomatic at birth - hearing defects and reduced intelligence.

Incidence of Cytomegalic Disease

	U.S.A.	U.K.
No. of live births p.a.	3,000,000	700,000
Rate of congenital CMV	1%	0.3%
No. of infected infants	30,000	2100
Symptomatic at birth (5 - 10%)	1,500-3,000	105
Fatal disease (˜20%)	300-600	22
No. with sequelae (90% of survivors)	1080-2160	83
Asymptomatic (90 - 95%)	27000	1995
No. with late sequelae	1350-4550	315

Diagnosis

- Isolation of CMV from the urine or saliva of the neonate.
- Presence of CMV IgM from the blood of the neonate.
- Detection of Cytomegalic Inclusion Bodies from affected tissue (rarely used)

Management

- Primary Infection - consider termination of pregnancy.
- 40% chance of the fetus being infected.
- 10% chance that congenitally infected baby will be symptomatic at birth or develop sequelae later in life.
- Therefore in case of primary infection, there is a 4% chance (1 in 25) of giving birth to an infant with CMV problems.
- Recurrent Infection - termination not recommended as risk of transmission to the fetus is much lower.
- Antenatal Screening – impractical.
- Vaccination - may become available in the near future.

Neonatal Herpes Simplex (1)

- Incidence of neonatal HSV infection varies inexplicably from country to country e.g. from 1 in 4000 live births in the U.S. to 1 in 10000 live births in the UK.
- The baby is usually infected perinatally during passage through the birth canal.
- Premature rupturing of the membranes is a well recognized risk factor.
- The risk of perinatal transmission is greatest when there is a florid primary infection in the mother.
- There is an appreciably smaller risk from recurrent lesions in the mother, probably because of the lower viral load and the presence of specific antibody.
- The baby may also be infected from other sources such as oral lesions from the mother or a herpetic whitlow in a nurse.

Neonatal Herpes Simplex (2)

- The spectrum of neonatal HSV infection varies from a mild disease localized to the skin to a fatal disseminated infection.
- Infection is particularly dangerous in premature infants.
- Where dissemination occurs, the organs most commonly involved are the liver, adrenals and the brain.
- Where the brain is involved, the prognosis is particularly severe. The encephalitis is global and of such severity that the brain may be liquefied.
- A large proportion of survivors of neonatal HSV infection have residual disabilities.
- Acyclovir should be promptly given in all suspected cases of neonatal HSV infection.
- The only means of prevention is to offer caesarean section to mothers with florid genital HSV lesions.

Parvovirus

- Causative agent of Fifth disease (erythema infectiosum), clinically difficult to distinguish from rubella.
- Also causes aplastic crisis in individuals with haemolytic anaemias as erythrocyte progenitors are targeted.
- Spread by the respiratory route, 60-70% of the population is eventually infected.
- 50% of women of childbearing age are susceptible to infection.

Congenital Parvovirus Infection

- Known to cause fetal loss through hydrops fetalis; severe anaemia, congestive heart failure, generalized oedema and fetal death
- No evidence of teratogenecity.
- Risk of fetal death highest when infection occurs during the second trimester of pregnancy (12%).
- Minimal risk to the fetus if infection occurred during the first or third trimesters of pregnancy.
- Maternal infection during pregnancy does not warrant termination of pregnancy.
- Cases of diagnosed hydrops fetalis had been successfully treated in utero by intrauterine transfusions and administration of digoxin to the fetus.

Varicella-Zoster Virus

- 90% of pregnant women already immune, therefore primary infection is rare during pregnancy
- Primary infection during pregnancy carries a greater risk of severe disease, in particular pneumonia

First 20 weeks of Pregnancy

up to 3% chance of transmission to the fetus,

recognised congenital varicella syndrome;

- Scarring of skin
- Hypoplasia of limbs
- CNS and eye defects
- Death in infancy normal

Neonatal Varicella

- VZV can cross the placenta in the late stages of pregnancy to infect the fetus congenitally.
- Neonatal varicella may vary from a mild disease to a fatal disseminated infection.
- If rash in mother occurs more than 1 week before delivery, then sufficient immunity would have been transferred to the fetus.
- Zoster immunoglobulin should be given to susceptible pregnant women who had contact with suspected cases of varicella.
- Zoster immunoglobulin should also be given to infants whose mothers develop varicella during the last 7 days of pregnancy or the first 14 days after delivery.