Congenital Viral Infections

An Overview
## Congenital, Perinatal, and Neonatal Viral Infections

### Intrauterine Viral Infections
- Rubella
- Cytomegalovirus (CMV)
- Parvovirus B19
- Varicella-Zoster (VZV)
- 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
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, microophthalmia, glaucoma, severe myopia) Other Defects (microcephaly, diabetes mellitis, thyroid disorders, dermatoglyptic abnormalities

Developmental
- Sensorineural deafness, Mental retardation, Diabetes Mellitus, thyroid disorder
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.
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.
Cytomegalovirus

INTRODUCTION

- Cytomegalovirus (CMV) infections were first described in the early years of the twentieth century when the typical ‘owl’s eye’ intranuclear inclusions were found by histopathologists in tissues from foetuses stillborn following cytomegalic inclusion disease.

- The virion of HCMV has typical herpesvirus structure, although somewhat larger, at 200 to 300 nm diameter.

  Growth In Vitro

- The only cells which replicate CMV to high titre in vitro are human fibroblasts, This finding is in complete contrast to that in vivo where cells infected with CMV are found in organs of epithelial origin
Cytomegalovirus

- Primary infection usually asymptomatic. Virus then becomes latent and is reactivated from time to time.

- CMV is spread by saliva, transplacental, breast milk, sexually and through infected blood.

- 60% of the population eventually become infected. In some developing countries, the figure is up to 95%.

- Transplacental infections occur in women who were infected before conception (recurrent infection) as well as in those who have primary CMV infection during pregnancy.
Transmission of CMV through the placenta barrier and infection of the fetus

Infected mother ➔ viraemia ➔ infection of placenta trophoblasts ➔ Infection of the oropharynx ➔ Virus in amniotic fluid ➔ Fetal viruria ➔ Viral replication in target organs (kidney) ➔ Infection of fetal endothelial cells ➔ Fetal viraemia
Intrauterine Infection

As is the case with rubella, intrauterine infection is assumed to follow maternal viraemia and subsequent placental infection, although this has not been proved formally. Due to the lack of maternal illness it has not been possible to identify a series of pregnant women with primary CMV infection and show that viraemia is a risk factor for 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 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.
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.
- Vaccination - may become available in the near future.
Antiviral Therapy for Congenital CMV Infection?

- Ganciclovir has been shown to be effective therapy for certain CMV infections in immunocompromised hosts (e.g., retinitis or enterocolitis in HIV-infected patients)

- Neonatal experience with ganciclovir is limited, the toxicity of the drug is considerable (e.g., platelets, neutrophils)
How is congenital CMV prevented?

- Many different ways to prevent CMV
- Our approach:
  - Hygiene, especially handwashing
  - Education about CMV and how to prevent it through hygiene
Herpes Simplex

- Herpes simplex virus (HSV) is a common human pathogen.

- HSV causes a wide range of diseases such as orolabial infections, pharyngitis and keratoconjunctivitis in humans.
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.

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.
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.
Parvoviruses are, as their name suggests, small viruses (from the Latin, parvum meaning small), with a singlestranded DNA genome. To date there is only one known human pathogen (parvovirus B19) in this entire family of viruses.

In electron micrographs of negatively stained preparations, parvovirus B19 appear as non-enveloped, icosahedral particles with a diameter of 18–25 nm

Transmission

Although spread from respiratory tract to respiratory tract is the common route of transmission of B19 virus, the high-titre viraemia which occurs during infection can lead to transmission by blood and blood products.
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.
- 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

Varicella-zoster virus (VZV) is a human alphaherpesvirus that causes varicella, commonly called chickenpox, during primary infection. Varicella, which is characterized by fever and a generalized, vesicular rash, is most prevalent in childhood.

- **Virion Structure**

  VZV particles, as those of the other herpesviruses, comprise four major elements: the core, the nucleocapsid, the tegument, and the envelope.

  For all alphaherpesviruses examined, including VZV, the initial attachment of particles to the cell surface appears between viral envelope glycoproteins and cellular surface glycosaminoglycans such as heparan sulfate.
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
  - CNS and eye defects
  - Death in infancy normal
Pathogenesis

- Highly contagious infectious agent
- Easily cultured from skin lesion of patients
- Transmitted from person to person by direct contact with the vesicular fluid of the skin lesions and/or by secretions from the respiratory tract
Host Response to Infection

- Following infection with VZV, antibodies are produced to the various structural and non-structural proteins of VZV. Up to 30 protein bands can be detected with convalescent sera by radioimmunoprecipitation or immunoblotting. Although specific antibody against VZV may protect against or attenuate infection, control of primary infection and clearance of virus appears to depend on cellular immunity.
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.
Preventive Methods

- Active immunization of seronegative women before pregnancy is recommended for effective prophylaxis of varicella in pregnant women and neonates.

- As all live-attenuated vaccines, varicella vaccine is contraindicated in pregnant women and pregnancy has to be avoided for at least 4 weeks following vaccination.
Therapeutic Measures

- An antiviral treatment has immediately to be introduced at first signs of varicella pneumonia or other disseminated infections.
- Aciclovir has to be administered orally at a dosage of $5 \times 800$ mg or intravenously at a concentration of $3 \times 10^{\text{–}15}$ mg/kg for 7–10 days.
- Zoster during pregnancy should only be treated with aciclovir in severe courses of the disease.