



MICROBIOLOGY

☐ Sheet

☒ Slide

☐ Handout

Number

2

Subject

Congenital viral infections

Doctor

Ashraf

Date: 00/00/2016

Price:

Congenital viral infections

Dr. Ashraf Khasawneh

Consequences of Infection

- Consequences to the infected host
 - Acute manifestations, chronic infection, other sequelae
- Vertical Transmission
 - Mother to infant
- Horizontal transmission
 - Family, close contacts, healthcare workers

Intrauterine Infection

Infections in pregnancy are common:

Which infections, if acquired in pregnancy,
may harm the fetus ?

Definitions

- congenital
 - contracted *in utero*
- perinatal
 - Fetal deaths beginning at 22 completed weeks (154 days) plus deaths of live births within the first seven days after birth. Live births eligible to be considered as perinatal deaths must be at least 500 g, or 22 completed weeks of gestation, or 25 cm in body length to be included in US perinatal statistics. For international perinatal mortality statistics, live births must have been either 1000 g or 28 completed weeks gestation or 35 cm in body length
- postnatal
 - period beginning immediately after the birth of a child and extending for about six weeks
- Neonatal
 - the first 28 days of life

Effect of Maternal Infection upon the fetus

- No evidence of damage
- Subclinical infection without evidence of damage
- Abortion
- Fetal death
- Stillbirth
- Death in infancy
- Intrauterine growth retardation (IUGR) resulting in low birth weight (LBW)
- Congenital defects
- Late onset of congenital disease or defects

Congenital and Perinatal Infection

1. Diagnosed *in utero*
2. Congenital infection may be asymptomatic or symptomatic at birth
3. Infection acquired around the time of birth may manifest later

Common Infecting Agents

- Viruses
 - Bacteria
 - Protozoa
 - Rickettsiae/Chlamydiae
-
- (Fungi are very very rare, as a cause of intrauterine infection – an increasing cause of late-onset neonatal sepsis)

Intrauterine & Perinatal Infection

Diagnosed *in utero*

Parvovirus B19

Manifest at Birth

Toxoplasma gondii

Cytomegalovirus

Treponema pallidum

hepatitis C

Rubella

Varicella/Zoster

hepatitis B

HIV

Intrauterine & Perinatal Infection

Acquired around the time of birth and symptomatic later

Herpes simplex

hepatitis B

hepatitis C

HIV

Group B β haemolytic streptococci

E. coli (+)

Listeria monocytogenes

Chlamydia trachomatis

Neisseria gonorrhoea

Torch Syndrome

Toxoplasma

Others (*Varicella/Zoster & Tr. Pallidum*)

Rubella

CMV

Herpes simplex

- CHEAPTORGES, was proposed by Ford-Jones and Kellner in 1995:
- C – Chickenpox and shingles
- H – Hepatitis B, C, (D), E
- E – Enteroviruses
- A – AIDS (HIV infection)
- P – Parvovirus B19
- T – Toxoplasmosis / Toxoplasma gondii
- O – Other (Group B Streptococcus, Listeria, Candida, Lyme disease)
- R – Rubella
- C – Cytomegalovirus
- H – Herpes simplex
- E – Everything else sexually transmitted (Gonorrhea, Chlamydia, Ureaplasma urealyticum, Human papillomavirus)
- S – Syphilis

Prevention

- Requires a knowledge of the route and mechanisms of infection, and the period of transmission of infection to the fetus/neonate

Intrauterine and Perinatal Infection

Mechanisms:

- Intrauterine
 - Blood borne transplacental infection
 - Ascending infection
- During delivery
- Postnatal infection
 - Breast milk
 - Cross infection
 - Environmental

Period of transmission

Virus	Congenital	Natal	postnatal
Rubella	+	-	-
Cytomegalovirus	+	+	+
Varicella-zoster	+	+	-
<i>Herpes simplex</i>	+	+	+
Hepatitis B	+	+	+
HIV	+	+	+

* *Principal time of transmission*

Intrauterine Infection:

What you should know

- The risk posed by the agent to the fetus
- Timing of infection in relation to risk
- Frequency of Damage
- Nature of Damage
- Availability of diagnostic tests
- Whether treatment is available
- Preventive measures

Protect the mother and the fetus

- Education
- Medical
 - standard precautions
 - Hand Hygiene
 - Personal Protective Equipment
 - Needlestick and Sharps Injury Prevention
 - Respiratory Hygiene
 - Safe Injection Practices
 - Serological screening
 - Screening for GBS carriage (controversial outside North America and AUS)

Antenatal screening

Definition:

- The systemic application of a test or enquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among people who have not sought medical attention on account of symptoms of that disorder

Antenatal Screening: Justification

- **Will give information “for action” to prevent or reduce the adverse consequences of the infection**
- **Treatment or prophylactic measures will usually be instituted**

Problems with screening for infection: it gives a “snapshot” in time

- **Women remain at risk of acquiring infection during the pregnancy - ? Repeat tests**
- **A woman may be in the “window period” before signs of the infection appear**

Examples of types of Congenital Infection - Included in routine antenatal screening programmes?

YES

Rubella

HBV

HIV

Syphilis

NO

CMV

herpes simplex

parvovirus B₁₉

Congenital Infection: specific examples

Rubella

An RNA togavirus

- 1938 viral aetiology suggested
- 1941 McAlastair Greig suggested an association between maternal rubella, congenital heart disease and cataracts
- 1962 virus isolated
- 1967 Serological tests available
- 1969 live vaccine developed

Rubella (German measles)

- Togavirus family, rubivirus genus.
- Enveloped, icosahedral, +ve ss-RNA genome
- Two glycoproteins E1 and E2
- One serotype, only in humans.
- Agglutinates chicks RBC's, Trypsin treated human type O RBC's.
- Virus enter the cell by viropexis. Genomic RNA encodes for nonstructural proteins and subgenomic RNA for structural proteins. Assembly occurs at the golgi or cytoplasmic membrane.
- Profound effects on developing fetuses.

Epidemiology and pathogenesis

- Winter and spring
- Women of childbearing age, carry a risk of exposure during pregnancy
- Contagious 7 days before to 7 days after onset of rash
- Infected babies spread the virus 6 M after birth.
- Spread by respiratory droplets
- URT, LNs, viremia, skin and organs.
- In the prevaccination era, 80% of women were already infected by childbearing age
- Maternal viremia, placental infection, spread to fetus and congenital infection.
- Pathogenesis of congenital defects: 1) vasculitis with impaired fetal oxygenation.
2) chronic viral infection leads to impaired mitosis, cellular necrosis and chromosomal breakage.
- Shedding of the virus in infected infants is prolonged (up to 30 months)
- Produce IgM and IgG antibodies to the virus, decrease to undetectable levels in 3-4 yrs.

Clinical Features

Rubella in a pregnant woman may be asymptomatic or characterized by:

- Fever
- URT symptoms
- conjunctivitis
- Lymph Node enlargement (post cervical and postauricular).
- Macular rash 1-3 days (head, neck and trunk), faint rash
- Complications: arthralgia, arthritis (up to 60% of cases)

Rash of Rubella



Risks of rubella infection during pregnancy

Preconception	minimal risk
0-12 weeks	>80% risk of fetus being congenitally infected resulting in major congenital abnormalities in all infants (heart defects and deafness). Spontaneous abortion occurs in 20% of cases.
13-16 weeks	infection 54%. 35% congenital abnormalities (deafness and retinopathy)
after 16 weeks	normal development. No congenital abnormalities

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.

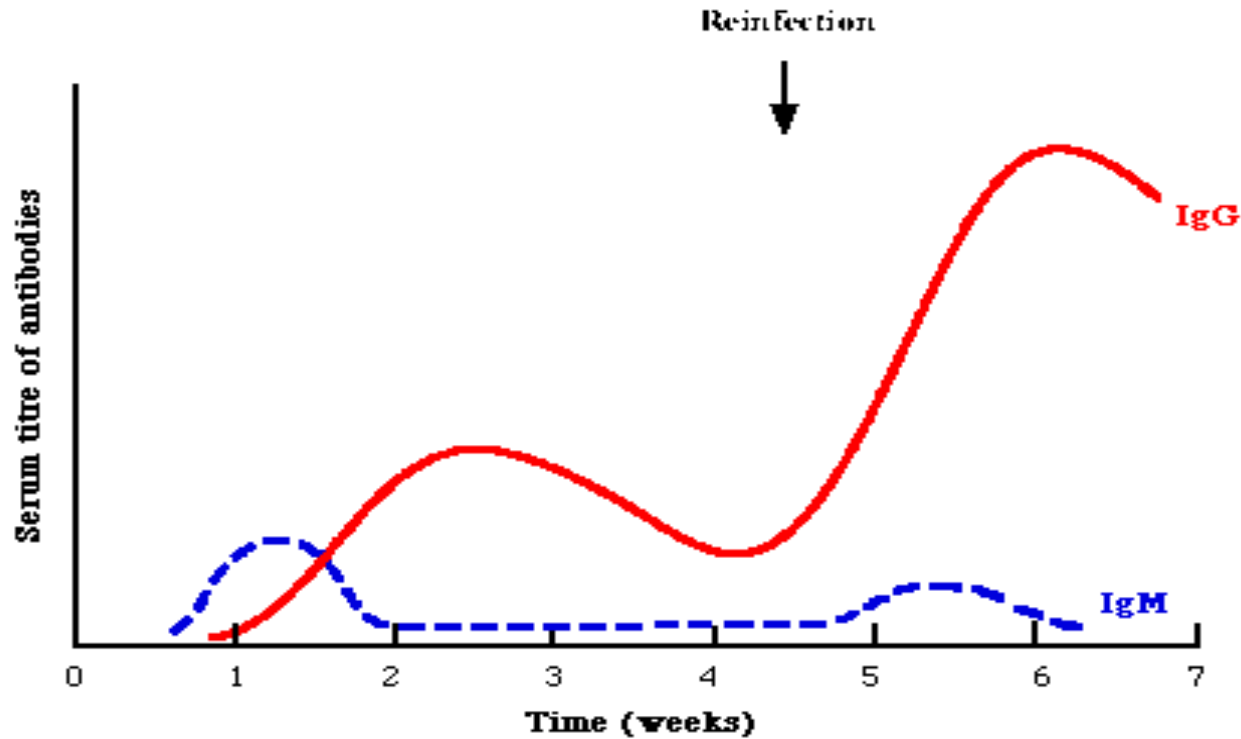
Transient	low birth weight, hepatosplenomegaly, thrombocytopenic purpura bone lesions, meningoencephalitis, hepatitis, haemolytic anemia pneumonitis, lymphadenopathy
Permanent	Sensorineural deafness, Heart Defects (peripheral pulmonary stenosis, pulmonary valvular stenosis, patent ductus arteriosus, ventricular septal defect) Eye Defects (retinopathy, cataract, microphthalmia, glaucoma, severe myopia) Other Defects (microcephaly, diabetes mellitus, 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”

Typical Serological Events following acute rubella infection



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

Laboratory Diagnosis

Diagnosis of acute infection

- Rising titres of antibody (mainly IgG) - HAI, EIA; ≥ 4 -fold rise between acute and convalescent sera
- Presence of rubella-specific IgM – EIA
- Viral detection via culture and/or reverse transcriptase–PCR (RT-PCR) of amniotic fluid, nose, throat (preferred), urine, CSF, or blood specimens
- Infant antibody titers (measured serially) and viral detection

In specialised centres diagnoses can be made prenatally by detecting:

- The virus in amniotic fluid
- Rubella-specific IgM in fetal blood
- Applying RT-PCR techniques to fetal blood or chorionic villus biopsy specimens.

Other tests include a CBC with differential, CSF analysis, and x-ray examination of the bones to detect characteristic radiolucencies. Thorough ophthalmologic and cardiac evaluations are also useful

Treatment

- Counseling: Women exposed to rubella early in pregnancy should be informed of the potential risks to the fetus
- Immune globulin for the mother
 - It does not prevent infection, and the use of immune globulin should be considered only in women who decline pregnancy termination

Prevention

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.
- MMRV: RA 27/3 human diploid fibroblast cell culture, female adults, hospital staff at risk, seroconversion in 95%
- Contraindications: IC and pregnant women
- Avoid conception for 1-3 months

Cytomegalovirus

The most common congenital infection worldwide;
predominantly due to primary maternal infection

Properties

- Belong to the betaherpesvirus subfamily of herpesviruses
- double stranded DNA enveloped virus
- Nucleocapsid 105nm in diameter, 162 capsomers
- 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
- Transmission may occur in utero, perinatally or postnatally. Once infected, the person carries the virus for life which may be activated from time to time, during which infectious virions appear in the urine and the saliva.
- Reactivation can also lead to vertical transmission. It is also possible for people who have experienced primary infection to be reinfected with another or the same strain of CMV, this reinfection does not differ clinically from reactivation.

Clinical Manifestations

- Congenital infection - may result in cytomegalic inclusion disease
 - 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.
 - Clinically apparent disease in the neonate is much more likely to occur after a primary maternal exposure particularly in the first half of pregnancy
 - May be transmitted to the fetus during all stages of pregnancy.
 - No evidence of teratogenicity, damage to the fetus results from destruction of target cells once they are formed.
- Perinatal infection - acquired by exposure to infected cervical secretions, breast milk, or blood products. Maternal antibody is thought to be protective, and most exposed term infants are asymptomatic or not infected
- Postnatal infection - usually asymptomatic. However, in a minority of cases, the syndrome of infectious mononucleosis may develop which consists of fever, lymphadenopathy, and splenomegaly. The heterophil antibody test is negative although atypical lymphocytes may be found in the blood.

Clinical manifestations

- Many women who become infected with CMV during pregnancy are asymptomatic, but some develop a mononucleosis-like illness.
- About 10% of infants with congenital CMV infection are symptomatic at birth
- Infants who acquire CMV after birth, especially if they are premature, may develop a sepsis-like syndrome, pneumonia, hepatosplenomegaly, hepatitis, thrombocytopenia, and atypical lymphocytosis.
- If transmission is via breast milk, the risk of severe symptomatic disease and long-term sequelae is low

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

- Viral culture using urine, saliva, or tissue
- PCR using urine, saliva, blood, or tissue

Congenital CMV is diagnosed if the virus is identified in urine, saliva, or other body fluids obtained within the first 3 wk of life; urine and saliva have the highest sensitivity. After 3 wk, viral detection may indicate perinatal or congenital infection

Other tests:

- CBC with differential and liver function tests may be helpful but are not specific.
- Cranial ultrasonography or CT and an ophthalmologic evaluation should also be done.
- Hearing tests should be routinely done at birth in all infected neonates, but close monitoring is required because hearing loss may be progressive

Prognosis

Symptomatic neonates have a mortality rate of up to 30%, and 40 to 90% of survivors have some neurologic impairment, including:

- Hearing loss
- Intellectual disability
- Visual disturbances

Among asymptomatic neonates, 5 to 15% eventually develop neurologic sequelae; hearing loss is the most common.

Management

- **Congenital infections** - it is not usually possible to detect congenital infection unless the mother has symptoms of primary infection. If so, then the mother should be told of the chances of her baby having cytomegalic inclusion disease and perhaps offered the choice of an abortion.
- **Perinatal and postnatal infection** - it is usually not necessary to treat such patients.
- 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.
- Treatment - There is limited evidence that treatment of infants with neurologic symptoms, with ganciclovir iv x 6 weeks, may help, however when the drug is stopped the viral load increases again. treatment is reserved for neonates with symptomatic CNS disease.
- Antenatal Screening – impractical.
- Vaccination - may become available in the near future.

Prevention

- Nonimmune pregnant women should attempt to limit exposure to the virus. For instance, because CMV infection is common among children attending day care centers, pregnant women should always wash their hands thoroughly after exposure to urine and oral or respiratory secretions from children.
- Transfusion-associated perinatal CMV disease can be avoided by giving preterm neonates blood products from CMV-seronegative donors or leukoreduced products.