OBSTETRIC AND PERINATAL INFECTIONS

- During pregnancy certain infections in the mother can be more severe or can reactivate.
- In addition a novel set of potentially susceptible tissues appear, including the foetus, the placenta and the lactating mammary glands.
- On the other hand, the placenta acts as an effective barrier, protecting the foetus from most circulating microorganisms, along with the fetal membranes.
- Perforation of the amniotic sac, for instance, at a late stage of pregnancy, often results in fetal infection.
- A few infections occur at around **the time of birth**. The infant may be directly exposed during passage down a birth canal that is infected with **gonococci, chlamydia or herpes simplex virus,** or is contaminated with **faecal bacteria** from the mother.
- **In the immediate post-natal period**, the mother's blood (hepatitis B virus) or milk (HTLV1) can also be a source of infection.

INFECTIONS OCCURRING IN PREGNANCY

- The foetus may be considered as an immunologically incompatible transplant which must not be rejected by the mother.
  - Reasons for the failure to reject the foetus include **absence or low density of MHC antigens on placental cells**, covering of antigens with blocking antibody, and subtle defects in maternal immune responses.
  - **A severe or generalized immunosuppression in the mother** would be undesirable because it would mean potentially disastrous susceptibility to infectious disease.
  - **Certain infections**, however, are known to be more severe and certain persistent infections reactivate **during pregnancy.**
  - **The hormonal changes** that accompany pregnancy can also increase susceptibility.
  - The picture is further complicated when there is **malnutrition**, which in itself impairs host defences by weakening immune responses, decreasing metabolic reserves and interfering with the integrity of epithelial surfaces.
- Once the foetus in infected it is susceptible. Its immune defences are poor; **IgM and lgA antibodies** are not produced in significant amounts until the second half of pregnancy, there is no **IgG antibody** synthesis, and cell-mediated immune responses are poorly developed or absent, with inadequate production of the necessary cytokines.
- Most microorganisms have sufficient destructive activity to kill the foetus, leading to **spontaneous abortion, or still- birth**.

I. CONGENITAL INFECTIONS

- After primary infection during pregnancy, certain microorganisms enter the blood, establish infection in the placenta, and then invade the foetus.
  - **The foetus sometimes dies, leading to abortion**,
  - but when the infection is less severe, as in the case of a relatively non-cytopathic virus, or when it is partially controlled by the maternal IgG response, the foetus survives.
  - It may then be born with a **congenital infection**, often showing malformations or other pathological changes. **The infant is generally small** and fails to thrive.
  - It produces specific antibodies, but often, for instance with cytomegalovirus (CMV), fails to generate an adequate virus-specific cell-mediated immune response, remaining infected for a long period. Hence, **the lesions may progress after birth**.
- Important causes of congenital infections are shown below.

Congenital (in utero) infections

Microorganism	Effects
***Rubella* virus**	Congenital rubella
Cytomegalovirus	Congenital CMV-deafness, mental retardation
HIV	Congenital infection-childhood AIDS, about 1in 5 infants born to infected mothers are infected in utero
Varicella-zoster virus	Skin lesions, musculo-skeletal CNS anormalities, severe diseases in newborn if mother infected too late in pregnancy to have provided transplacentar IgG for foetus
Herpes simplex virus	Neonatal herpes simplex, often disseminated – infection in utero are rare
Hepatitis B virus	Congenital hepatitis B-persistent infection
Treponema pallidum	Congenital syphilis-classical syndrome
Toxoplasma gondii	Congenital toxoplasmosis
Mycobacterium leprae	Congenital infection common in mothers with lepromatous leprosy

- Viruses that induce **fetal malformations** (i.e. act as teratogens) share certain characteristics with **other teratogens, such as drugs or radiation**.

- The foetus tends to show similar responses to different infectious agents **(hepatosplenomegaly, encephalitis, eye lesions, low birth weight**), and the diagnosis is difficult on purely clinical grounds.

- Most of these infections (rubella, CMV, syphilis) can also, at times, kill the foetus. They generally follow **primary infection of the mother during pregnancy**, so that their incidence depends on the proportion of non-immune females of child-bearing age.

- Routine antenatal screening for antibodies to rubella, syphilis and HIV identifies susceptible (rubella) and infected (syphilis, HIV) mothers.

- In the case of CMV, reactivation of an earlier infection can occur during pregnancy and lead to fetal infection. Congenital syphilis can also result from earlier, untreated infection of the mother.

- There is no good evidence to suggest that maternal mumps, influenza or poliovirus infection during pregnancy leads to harmful effects in the foetus.

Congenital rubella

- The foetus is particularly susceptible when maternal infection occurs during the **first three months of pregnancy.** At this time the **heart, brain, eyes and ears are being formed and the infecting virus interferes with their development**. If the foetus survives it may show certain abnormalities. About 25% of congenitally infected children eventually develop **insulin-dependent diabetes mellitus**, but rubella is a very uncommon cause of this disease. The virus replicates in the pancreas.
- The classical features of congenital rubella infection were first described by Gregg in Australia in 1941, long before the virus had been isolated and characterized.
- Not all foetuses are affected; *in one study detectable congenital defects were seen in 15.3% of cases when maternal rubella occurred in the first month of pregnancy, 24.6% when in the second month, 17.5% in the third month and 6.5% in the fourth month.*
- Rubella causes malformations by a primary effect on blood vessels in the developing organs, and also a virus-mediated inhibition of mitosis which contributes to the reduced number of cells and the small size of rubella babies.

Diagnosis, treatment and management

- Clinical appearances include **low birth weight, eye and heart lesions**. Effects on the brain and ears may not become detectable until later in childhood in the form of **mental retardation and deafness**. There is a 15% mortality in infants showing signs of infection at birth, often associated with **hypogammaglobulinaemia**.
- Infected **foetuses produce their own IgM molecules to rubella virus**, which can be detected in cord blood. **Maternal IgG antibodies** are also present and, together with interferons, help to control the spread of infection in the foetus. Virus can be isolated from the infant's throat or urine.
- **There is no treatment**. The infant sheds virus into throat and urine for several months and can infect susceptible individuals.
- Congenital rubella is completely preventable by **vaccination** with live attenuated virus vaccine. This is done during childhood, usually with the combined **MMR** (mumps, measles and rubella) vaccine. Pregnancy is a contraindication to vaccination, and the only safe time during reproductive life is the immediate post-partum period.

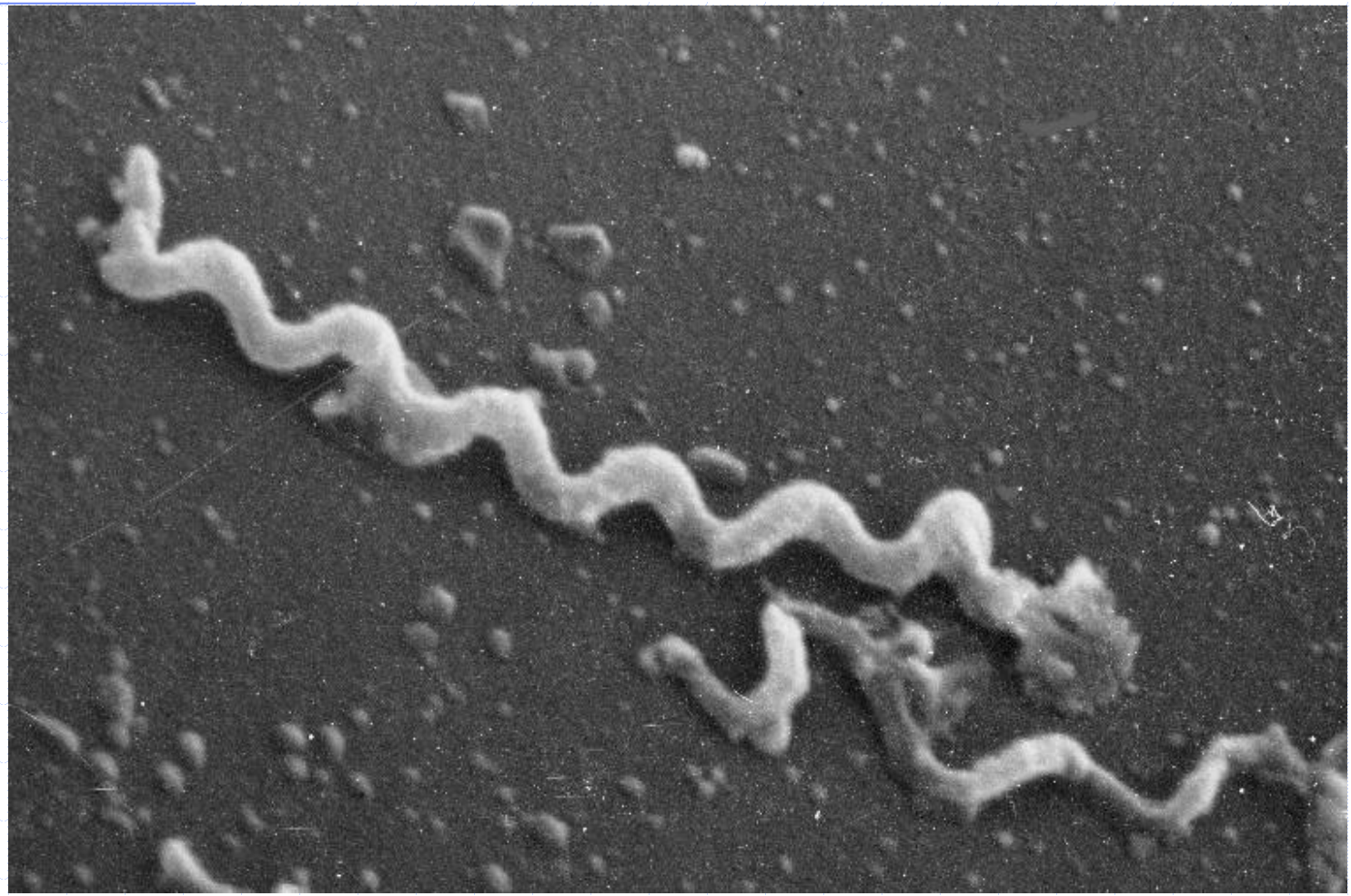
Congenital cytomagalovirus infection

- Clinical features of congenital CMV include **mental retardation, spasticity, eye abnormalities, hearing defects, hepatosplenomegaly, thrombocytopenic purpura and anaemia**. Mothers that develop a poor T cell proliferative response to CMV antigens are more likely to infect their foetus.
- After primary maternal infection during pregnancy about **40% of foetuses are infected and 5% of these show signs at birth**. It is not known whether the foetus is especially vulnerable at certain stages of pregnancy. The foetus is also infected following pregnancy, reactivation of CMV in immune (sero-positive) mothers, but fetal damage is then uncommon. **Deafness and mental retardation may not be detectable until later in childhood.**
- **Diagnosis and prevention**
- Diagnosis is by detecting CMV-specific IgM antibodies in cord blood, and more reliably by virus isolation from throat or urine. Live attenuated vaccines are presently being developed;

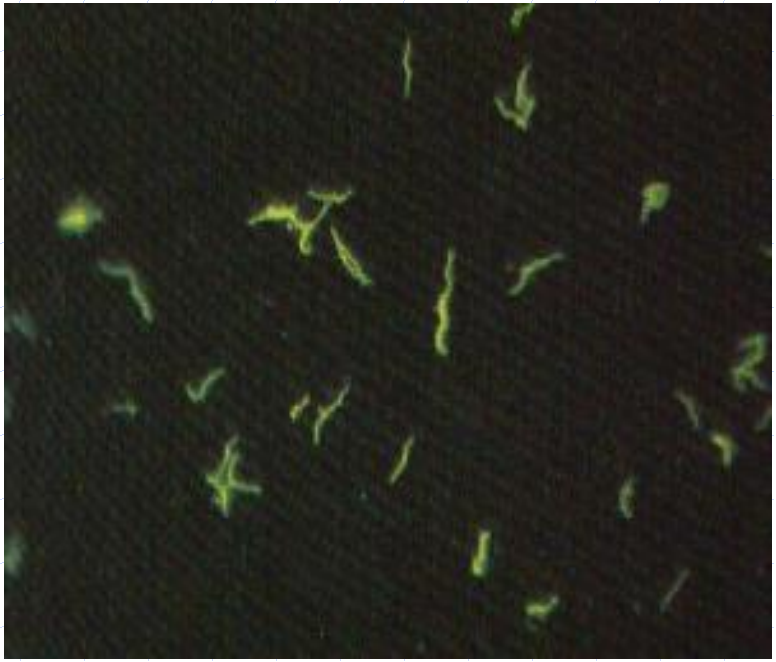
Congenital syphilis

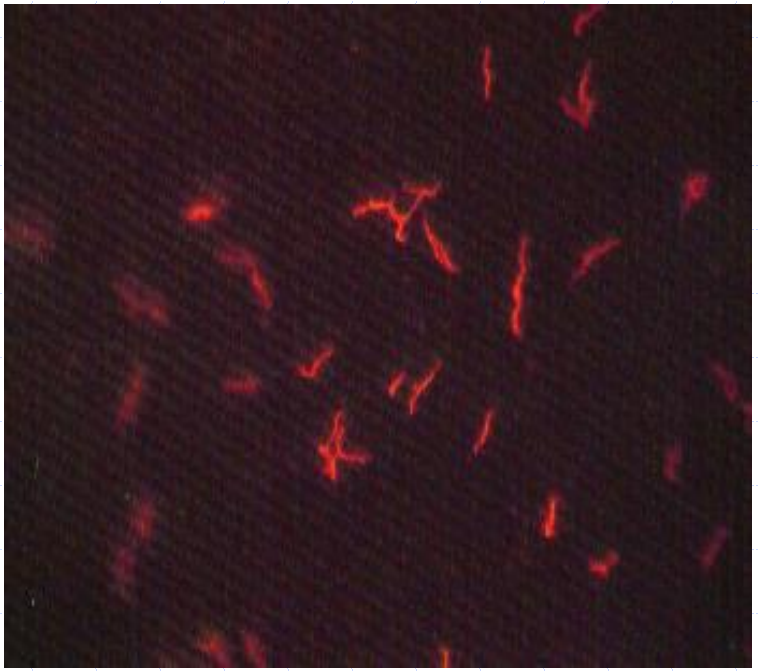
- As a result of routine serological screening for syphilis in antenatal clinics and treatment with penicillin , this condition is now rare but is more common in developing countries. Treatment of the mother before the fourth month of pregnancy prevents foetal infection.
- Clinical features in the infant include **rhinitis (snuffles), skin and mucosal lesions, hepatosplenomegaly, lymphadenopathy, abnormalities of bones, teeth, cartilage (saddle shaped nose),** etc. Pregnancy often masks the early signs of syphilis, but antibodies will be present in the mother, and *Treponema pallidum*-specific lgM antibodies in the foetus.

Treponema pallidum

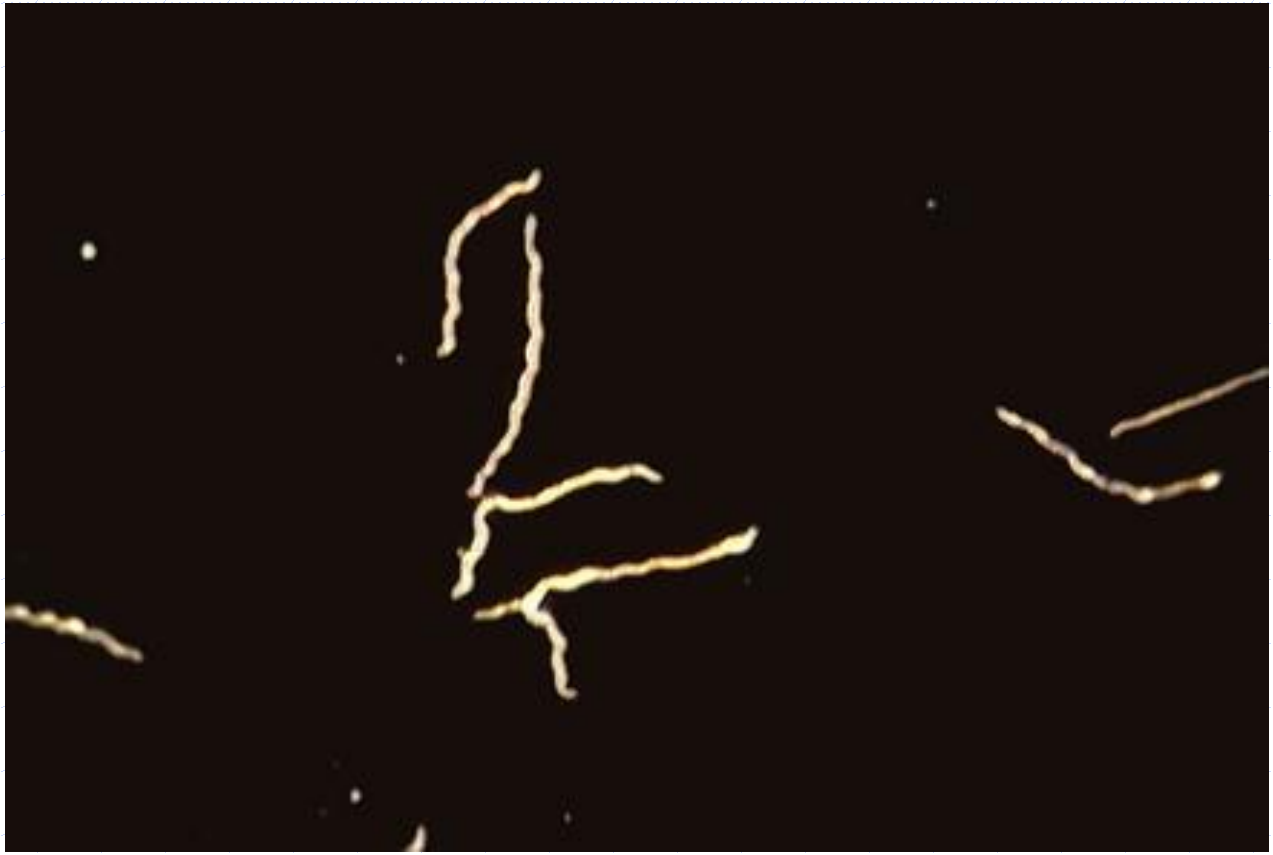


Imunofluorescens





Dark field microscopy



Congenital toxoplasmosis

- This results from acute, asymptomatic infection by *T.gondii* during pregnancy. About one-third of normal adults are seropositive. Clinical features in the infant include **convulsions, microcephaly, chorioretinitis, hepatosplenomegaly, jaundice, with later hydrocephaly, mental retardation and defective vision**. There are often no detectable abnormalities at birth but signs (e.g. chorioretinitis) generally appear within a few years. The incidence of foetal infection and damage (leading to abortion, stillbirth or disease in the newborn) increases from 14% when maternal infection is in the first trimester to 59% when in the third trimester.
- **Diagnosis, treatment and prevention**
- Toxoplasma-specific IgM antibodies may be detected in cord blood. Treatment of a pregnant woman or an infected infant is with spiramycin, or sulphonamide or pyrimethamine.
- There is no vaccine. Prevention is by avoidance of primary infection (via cysts from cat faeces or in lightly cooked meat) during pregnancy.

Congenital HIV infection

- At least 1 in 5 of infants born to HIV infected mothers are infected in utero. They show **poor weight gain, susceptibility to sepsis, developmental delays, lymphocytic pneumonitis, oral thrush, enlarged lymph nodes, hepatosplenomegaly, diarrhoea, pneumonia, and some develop AIDS within the first year.** Infection may also take place during or shortly after birth.
- Laboratory diagnosis is at present difficult . If IgG antibodies are present they will be of maternal origin and can persist for at least a year; there is no satis-factory test for HIV-specific IgM antibodies, which would signify in utero infection. Reliable blood tests for viral antigens or nucleic acid sequences would solve this problem.

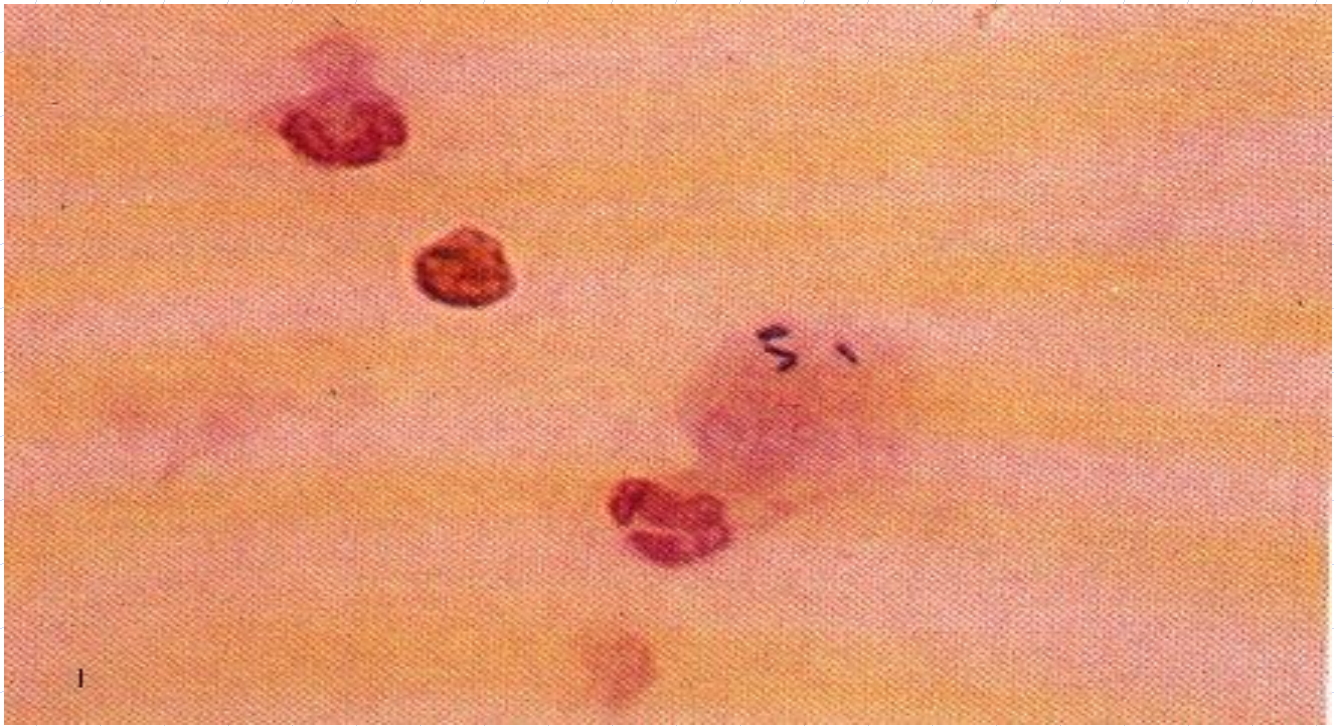
Congenital and neonatal listeriosis

- **Aetiology and transmission**
- *Listeria monocytogenes* is a small Gram-positive rod, which is motile and beta-haemolytic. It is **distributed world-wide in a great variety of animals including cattle, pigs, rodents and birds.**
- Transmission to man is **by contact with infected animals and their faeces**, or by **consuming unpasteurized milk or soft cheeses.**
- Up to 70% of people may carry listeria in the gut for short periods, without disease. Unlike most bacteria, *Listeria* can **grow at regular refrigeration temperatures** (e.g. 6ºC). The bacteria also occur in plants and in soil, and infection can be due to **eating contaminated vegetables.**

Clinical features and pathogenesis Diagnosis, treatment and prevention

- *Listeria monocytogenes* in the pregnant woman causes a **mild, influenza-like illness or is asymptomatic**.
- But there is a **bacteraemia**, which leads to **infection of the placenta and then the foetus. This may cause abortion, premature delivery, neonatal septicemia, pneumonia, with abscesses or granulomas**. The infant can also be infected shortly after birth, for instance from other babies or from hospital staff, and this may lead to a **meningitic illness**.
- *Listeria monocytogenes* is isolated from blood cultures, CSF or skin lesions. Treatment is with penicillin or ampicillin. There are no vaccines. Although pregnant women should not be exposed to infected material, the exact source of infection is generally unknown.

Microscopy



II. INFECTIONS OCCURRING AROUND THE TIME OF BIRTH

Effects on the foetus and neonate

- **Viral infections** (rubella, CMV) are generally less damaging to the foetus when maternal infection takes place late in pregnancy, but primary infection with varicella-zoster virus at this time can lead to limb deformities and other severe lesions in the newborn.

- **Bacterial infections** originating from the vagina and perineum are more important, occurring especially when foetal membranes have been ruptured for more than 1-2 days, and resulting in **chorioamnionitis, maternal fever, premature delivery and stillbirth**. Infants of low birth weight (less than 1500g) tend to be more severely effected.

  - **Bacteria** involved include **group B streptococci**, ***E. coli***, ***Klebsiella***, ***Proteus***, ***Bacteroides***, **staphylococci**, ***Mycoplasma hominis***. These infections may also be acquired after delivery, to give later onset disease.

  - **Neonatal septicaemia often progresses to meningitis** and this is frequently fatal unless treated. Clinical diagnosis is difficult because the infant shows generalized signs such as respiratory distress, poor feeding, diarrhoea and vomiting, but early diagnosis is essential and requires emergency treatment.

- **'Blind' antibiotic treatment should be started** as soon as CSF (Gram-stain and culture) and blood samples have been taken.
- The foetus can also be infected during labour by direct contact as it passes down an infected birth canal.
  - For instance, **cutaneous lesions of herpes simplex** may develop a week after delivery, with generalized infection and severe **CNS involvement,**
  - and **both gonococci, chlamydia or staphylococci can wipe the eye to cause ophthalmia neonatorum.**
  - **Maternal blood can be a source of hepatitis B virus** infection during or shortly after birth and 80-90% infants from HBV carrier mothers become infected and then carry the virus. This is preventable by giving the vaccine plus specific immunoglobulin to the newborn.
- **Human milk may contain rubella virus, CMV, HTLV1, and (probably) HIV**. Virus titres are generally low, and, except in the case of HTLV1, milk is not thought to be an important source of infection.

Effects on the mother

- After delivery (or abortion) a large area of damaged, vulnerable uterine tissue is exposed to infection.
- **Puerpural sepsis** (childhed fever) was a major cause of maternal death in Europe in the 19th Century. In 1843 Oliver Wendell Holmes made the unpopular suggestion that it was carried on the hands of doctors, and four years later **Ignaz Semmelweiss in Vienna** showed how it could be prevented if doctors washed their hands before attending a woman in labour and practised aseptic techniques.
- **Group A beta-haemolytic streptococci** were major culprits. Other possible organisms include anaerobes such as ***Clostridium perfringens or Bacteroides,*** **and** ***E. coli.*** The streptococci came from the nose, throat or skin of hospital attendants whereas the others were derived from the mother's own faecal flora.
- Puerpural sepsis, which carried up to 10% mortality until the 1930s, is now, like septic abortion, less common in developed countries.
- **Predisposing factors** include premature rupture of the membranes, instrumentation and retained fragments of membrane or placenta. Where there is postnatal pyrexia or offensive discharge, high vaginal swabs and blood cultures should be taken.

Miscellaneous neonatal infection

- Infection may reach the newborn infant during the first week or two after birth, rather than during delivery.
- **Group B beta-haemolytic streptococci and Gram-negative bacilli can still cause serious infection at this time, often with meningitis**.
- **Herpes simplex may come from cold sores or herpetic witlows** of attending adults.
- **Staphylococcal infection** from noses and fingers of adult carriers may cause staphylococcal conjunctivitis or 'sticky eye', skin sepsis in the neonate, and sometimes the staphylococcal 'scalded skin' syndrome due to a specific 'epidermolytic' staphylococcal toxin. During the first week or two of life the nose of the neonate becomes colonized with *Staphylococcus aureus* which can enter the nipple during feeding to cause a breast abscess. These infections are preventable when hospital staff pay vigorous attention to hand washing, aseptic techniques, and so on.
- The umbilical stump, especially in developing countries, may by infected with ***Clostridium tetani,*** resulting in neonatal tetanus. It can be prevented by immunizing mothers with tetanus toxoid.
- In developing countries gastroenteritis is an important problem during the neonatal period as well as during infancy. Diarrhoea leading to water and electrolyte depletion is particularly serious in low birth weight infants. Causative agents include strains of ***E. coli, Salmonella*** etc., rather than **rotaviruses**. Breast feeding gives some protection by supplying specific antibodies and other less well-characterized protective factors.