REVIEW
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Congenital and Neonatal Infections

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Abstract
Infections acquired in utero or during the birth process are a significant cause of fetal and neonatal mortality and an important contributor to early and later childhood morbidity. The original concept of the TORCH perinatal infections was to group five infections with similar presentations, including rash and ocular findings (1). This TORCH complex encompasses the infections caused by Toxoplasma gondii, rubella virus, cytomegalovirus, herpes simplex virus both types 1 and 2 and other infective organisms. This review will concentrate on the traditional TORCH infections with Syphilis, Parvovirus B 19, Group B Streptococci infection and Varicella discussed under 'Other Infections(8). Treatments each vary as discussed however no specific therapy for certain infections has yet been established, thus prevention protocols should be heeded to.

Introduction

During pregnancy infections that are either acquired or reactivated can affect the outcome of pregnancy.[1] TORCH syndrome is a unique acronym for (**T**)oxoplasmosis, (**O**)ther infections, (**R**)ubella, **(C**)ytomegalovirus) and (**H**)erpes Simplex virus type 2.[1] Klein and Remington[2] have suggested that this classification is too limiting and that several additional infectious agents should be considered in the Other category, such as enteroviruses, and Human Immunodeficiency Virus (HIV).

This review however will concentrate on the traditional TORCH infections with Syphilis, Parvovirus B 19, Group B Streptococci infection and Varicella representing 'Other Infections'.

Infection with any of these agents may cause a constellation of similar symptoms in affected newborns. These may include fever; difficulties feeding; small areas of bleeding under the skin, causing the appearance of small reddish or purplish spots; enlargement of the liver and spleen (hepatosplenomegaly); yellowish discoloration of the skin, whites of the eyes, and mucous membranes (jaundice); hearing impairment; abnormalities of the eyes; and/or other symptoms and findings. Each infectious agent may also result in additional abnormalities that may be variable, depending upon a number of factors (e.g., stage of fetal development).[1]

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Syphilis

Syphilis is a bacterial infection caused by the spirochete, *Treponema Pallidum*, a spiral shaped highly motile gram-negative bacteria that is transmitted during sexual activity.[3]

The clinical features are divided into a Primary and a Secondary stage.[3] The primary stage is marked by the appearance of a single ulcer (chancre).This lesion usually occurs on the external genitalia, vagina or anus and less commonly on the rectal and oral mucosa. It usually is accompanied by lymphadenopathy in 50% of cases. It usually lasts 3 to 6 weeks with spontaneous resolution.

If not treated, the infection can lead to a secondary infection. This is characterized by systemic manifestations, which appear about 2 to 6 weeks after the chancre resolves. This is characterized by skin rash, red or brown spots on the palms of hands and sole of feet, fever, sore throat, etc. These symptoms can resolve without treatment. The infection can lead to latent or tertiary syphilis if not treated & during pregnancy can lead to spontaneous abortion, stillbirth, non-immune hydrops fetalis, preterm birth, intrauterine restriction or congenital syphilis with multi-system manifestations, such as deafness, neurologic impairment and bone deformities.

According to the National Antenatal Seroprevalence Survey in 2012 the national prevalence of syphilis shows a 0.1% increase, where the prevalence was 1.5% in 2010 and 1.6% in 2011.[4] In Gauteng, there was a slight drop of 2.9% in 2009 to 2.0% in 2011.[4] World Health Organization initiative to eliminate mother-to-child transmission of syphilis aims for ≥90% of pregnant women to be tested for syphilis and ≥90% to receive treatment by 2015.[5]

Transmission of the infection to the fetus can occur transplacentally or during passage of the newborn through the birth canal by contact with a genital lesion.[3] Breast feeding does not result in syphilis transmission, unless an infectious lesion is present on the breast.[6] Transmission rates are between 25% and 64% for primary, secondary or early latent syphilis. Vertical transmission rates are around 10% in latent syphilis.[3] T Pallidum gains access to the fetal compartment as early as 9-10 weeks.[6] Prenatal diagnosis includes detection of IgM antibodies against T.Pallidum on fetal blood from cordocentesis or PCR of the amniotic fluid.[7,9] Ultrasound findings include hepatosplenomegaly, placentomegaly and dilatation of small bowel.[7]

Diagnosis is usually made using serological assays.[8] Dark field microscopy can be used if a chancre is present.[9,10] Tests are classified into non-treponemal tests, venereal disease research labarotory(VDRL) and rapid plasma regain(RPR) and the treponemal tests, fluorescent treponemal antibody absorption (FTA-ABS) and the micohaemagglutination assay for T pallidum antibody(MHA-TP). The non-treponemal tests become reactive 4 to 8 weeks after infection is acquired.[9,10] The sensitivity for the diagnosis of primary and latent and late syphilis is between 60-90%.[9] Secondary syphilis, the sensitivity is close to 100%. FTA-ABS is highly sensitive (85-100%) in all stages of the disease.[10]

Treatment for syphilis is according to the stage of disease. For primary, early or latent syphilis bezathine penicillin G, 2.4 million units intramuscularly is administered as a stat dose.[3,7,9,10]

Cytomegalovirus (CMV)

Cytomegalovirus is a DNA virus and humans are its only known host.[8] Transmission occurs by contamination of urine, saliva, blood and other secretions. It is a common cause of sensorineural hearing loss and mental retardation. Mother-to-child-transmission is mainly the result of primary maternal CMV infection which carries a risk of transmission varying from 24% to 75%.[11] Usually the patient is asymptomatic. If symptomatic the patients they may present with non-specific symptoms including malaise, fever, and generalized lymphadenopathy.[11] 10 to 15 % percent of congenitally infected infants will have symptoms at birth; 20-30% of them will die.[12]

If CMV is suspected, serologic assay for IgM and IgG antibodies are used to confirm the diagnosis.[8] The initial serology can be confusing because the IgM antibody can remain positive for up to 9 to 12 months after an acute infection. IgG avidity testing can be useful to differentiate between acute and chronic infection. Virus specific IgG of low avidity is produced during the first months after the infection. Subsequent maturation process forms IgG antibodies of increasingly higher avidity.[14]

Diagnosis of congenital infection is confirmed by CMV detection in amniotic fluid by PCR or culture. The diagnosis alone is not sufficient to predict newborn disease. Maternal viraemia has not been correlated with fetal or neonatal symptoms.[8] The amniocentesis should be done at least 7 weeks after the presumed time of maternal infection and after 21 weeks of gestation. The interval is important because it takes 5 to 7 weeks following fetal infection and subsequent replication of the virus in the kidney for a detectable quantity of the virus to be secreted in the amniotic fluid. Quantitative determination of CMV DNA in the amniotic fluid may assist in predicting the fetal outcome. Fetal CMV infection should be monitored by detailed ultrasound examination. Placentomegaly, IUGR, echogenic bowel, microcephaly, ventriculomegaly and periventricular calcifications.[12]

Therapy for pregnant women with primary infection remains inconclusive. Ganciclovir[14] or its oral form is reported in studies to have a decrease in viral load but the foetuses had a poor outcome. Awaiting the outcome of randomised control trials, consensus among many obstetricians that the off-label use of CMV human immunoglobin(HIG) should be offered as an alternative to termination of pregnancy, particularly if the is ultrasound evidence of fetal injury.[13] HIG may also be considered when there is a serologically confirmed primary CMV after conception and the maternal IgG avidity to CMV is low and amniotic fluid contains CMV or CMV DNA.[8]

Prevention includes regular hand washing especially after changing baby's nappies and handling toys. No commercially available vaccine is available. In 2008, the Centres for Disease Control and Prevention website recommended that pregnant child-care employees should have serologic test done and if seronegative should avoid caring for children less than 2 years of age for the duration of pregnancy.[15]

Genital Herpes Simplex Virus infection in Pregnancy

Genital herpes is caused by the herpes simplex virus type I (HSV -1) or type 2 (HSV-2).

The risk of neonatal infection is greatest when maternal primary infection occurs in the third trimester, when the infant is delivered in the absence of protective passive IgG from the mother resulting in a 30% to 50% risk of neonatal herpes infection.[16] Primary infection occurring in the first or second trimester usually does not affect the fetus. In rare cases transplacental transmission occurs resulting in congenital infection. Fetal manifestations include microcephaly, hepatosplenomegaly, IUGR and IUFD.

Management during pregnancy

Treatment with antivirals, including the first trimester of pregnancy, is usually appropriate if maternal symptoms are severe. If there is a primary infection present in the third trimester, caesarean section is indicated.

A women with recurrent herpes infection who does not have a lesion present at delivery has a small risk of

asymptomatic shedding (1%) and the risk of neonatal infection can be calculated to be 0.02% to 0.05%.[17] If a genital HSV lesion is present at the time of vaginal delivery, risk of neonatal infection is reported to be 2% to 5 %.[17] Any HSV lesions that appear in the mother postpartum should be managed with proper hand washing and contact precautions. Breastfeeding is contraindicated only if the woman has active lesions on the breast.[18]

American College of Obstetricians and Gynaecologists (ACOG) Practice Bulletin recommends that women with active recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation. Caesarean section is indicated in women with active genital lesions or prodromal symptoms such as vulvar pain or burning at delivery as these may indicate an impending outbreak.[16] The Royal College of Obstetricians and Gynaecologists recommends that women with recurrent genital lesions at the onset of labour not have a caesarean section. These women should be advised that the risk of neonatal herpes is small. Mode of delivery should be individualized.[17]

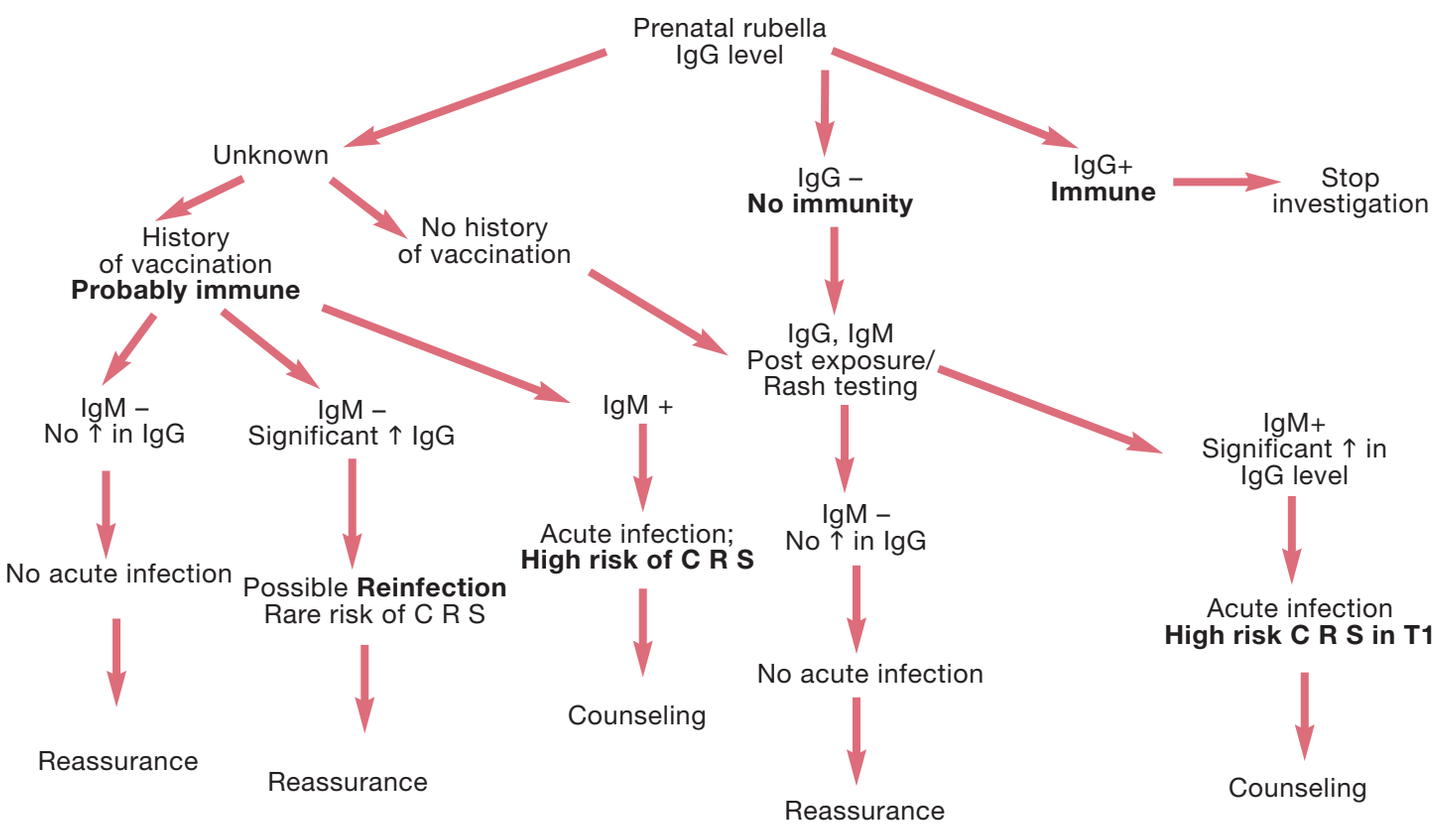
Rubella

Rubella is an enveloped RNA virus in Togaviridae family.[22] The virus is spread through direct or droplet contact from nasopharyngeal secretions. Individuals infected shed the virus 5 to 7 days before and 14 days after the infection. Congenital rubella occurs when a nonimmunized, susceptible, pregnant women is exposed to the virus. Transplacental infection occurs during the viraemic stage.[1] The greatest risk to the fetus is during the first trimester, which can result in serious consequences including miscarriages, stillbirths and a constellation of severe birth defects known as congenital rubella syndrome.

Primary Rubella infection is typically mild, sub-clinical disease in adults. The prodromal symptoms are characterized by low-grade fever, myalgia, headache, conjunctivitis, cough, sore throat and lymphadenopathy. Symptoms may last up to 4 days and often resolve with the appearance of a rash.

Women who are infected with Rubella in pregnancy exhibit minor clinical symptoms. The effects of Rubella on the fetus can be profound, with the greatest risk of malformation in early stages of pregnancy. Up to 85% of foetuses exposed to rubella in the first trimester develop serious sequelae. Little, if any risk of CRS is associated with infection beyond 20 weeks; and fetal growth restriction seems to be the only sequel of third trimester infection.[23] Congenital defects and late manifestations of Rubella Infection include sensorineural deafness, cardiac defects, ophthalmic defects, retinopathy and cataracts, central nervous system defects, mental retardation and microcephaly. Late expression of CRS includes progressive pan-encephalitis, pneumonitis, diabetes mellitus and thyroid dysfunctions.[22] Sensorineural deafness can occur up to 19th week gestation and may become evident later in childhood.[23]

Algorithm for the Management of Rubella in an exposed pregnant women[25]



It is estimated that approximately 660 cases occur annually in South Africa.[21] Acquired and congenital rubella is not a notifiable disease in SA. Routine Rubella vaccine does not form part of the Expanded Programme for Immunization (EPI) in SA.

Diagnosis is confirmed by the presence of Rubella-specific IgM. This can usually be detected 4-30 days after the onset of illness. Blood should be taken as early as possible after the onset of illness. In cases of suspected rubella and IgM-negative, usually taken before day 5; the specimen should be repeated after day 5. Diagnosis of fetal infection involves taking CVS at 10-12 weeks or amniotic fluid between 14 to 16 weeks. The sample is sent for rubella-specific PCR. It is important to note that ultrasound diagnosis is extremely difficult.[24]

Treatment is supportive. No data supporting the use of immunoglobulin in pregnant women with acute infection in order to diminish the fetal response to disease. The Centre for Disease Control recommends limiting use to women with known rubella exposure who decline pregnancy termination.[24]

Prevention with the Rubella vaccine is typically administered as part of a three-fold vaccine (MMR) at 12 to 15 months of age and again at 4 to 6 years of age. Any women receiving the rubella vaccine should not become pregnant for 28 days.

Toxoplasmosis

Toxoplasmosis is a disease caused by the intracellular protozoan parasite Toxoplasma gondii (T gondii), when acquired prenatally poses a significant risk to the fetus.[25] The incidence and severity depends on the timing of maternal infection. Transmission rates vary from < 5% early in pregnancy to > 80% by end of pregnancy[26], however severity of infection occurs with first trimester infection.

In the neonates, congenital toxoplasmosis might include[27]:

- Hydrocephalus, microcephaly& intracranial calcifications,
- retinochoroiditis, strabismus & blindness
- epilepsy, psychomotor & mental retardation,
- petechiae due thrombocytopenia, and anemia

Prenatal diagnosis includes a serological diagnosis of primary maternal infection, which is a challenge, as IgM antibodies might persist many years post primary infection. IgG titers and repeat testing as well IgG avidity testing are helpful to distinguish acute from previous infection. If acute infection is suspected while both IgM and IgG antibodies are positive repeat testing in 2 to 3 weeks is recommended, a 4 fold rise IgG antibody titre indicate recent infection.[26]

There is insufficient evidence to prove that treating mothers with seroconversion during pregnancy reduce fetal infection, however treatment might reduce the severity of congenital toxoplasmosis.[28] Spiromycin is a macrolide antibiotic that cannot cross the placenta but remains concentrated in it, is a drug of choice to prevent vertical transmission.[26] Fetal infection is confirmed by amniotic fluid PCR, and is treated with pyrimethazine and sulfadiazine.[29]

Prevention is mainly by educating pregnant women to avoid the source. In humans, the infection is acquired by consumption of uncooked or raw meat of infected animals and contaminated food by T gondi oocytes excreted in faeces by infected cats.[26]

Parvovirus B19

Parvovirus B19 is a small non-enveloped DNA virus, spread by respiratory droplets, with a clinical manifestation that vary from benign to life threatening. Clinical presentation includes erythema infectiosum (mainly childhood infection), arthropathy, transient aplastic crisis and pure red blood cell aplasia in susceptible individuals, as well as fetal infection.[30]

The incidence of B19V infection during pregnancy is 3.3-3.8%.[31] Transplacental transmission occurs in an estimated 35% of infected pregnant mothers and it is reported to be during maternal peak viral load that is 1-3 weeks after maternal infection.[32] Most intrauterine B19V infections do not have adverse outcome, and developmental delays are no more frequent in offspring of actively infected mothers compared with uninfected mothers.[31]

Fetal manifestations include:

1) Nonimmune hydrops fetalis (NIHF) - thought to result from severe anemia. B19V preferentially infects rapidly dividing cells and is cytotoxic for erythroid progenitor cells.[33] The fetus is most vulnerable in the hepatic stage (8-20 weeks) of hematopoietic activity.[34]
2) Severe thrombocytopenia is a common finding in hydropic, anemic B19V infected fetuses.[32]
3) Transient effusions- isolated pleural or myocardial effusions that resolve spontaneously have been reported and are thought to be due to direct myocardial or pleural inflammation.[31]
4) Fetal death and miscarriages.

In a large prospective study of B19 infection in 1018 pregnant women with acute infection based upon serological studies major findings included[35]:

- fetal death occurred in 6.3% of pregnancies (64/1018) and was limited to B19 infection diagnosed in the first half of pregnancy
- the death rate in the first trimester was 13% (34/256); 9% (30/222) in 13-20 weeks gestation and none after 20 weeks gestation.
- there were total of six stillbirths, four prior to 24 weeks and two at term (the term stillbirths not attributed to B19)

Maternal acute infection is confirmed by a positive IgM antibody serology test or a more sensitive PCR test for B19V DNA.[32] PCR of amniotic fluid is method of choice for diagnosis of fetal infection. Other option is fetal blood for

B19V IgM testing, however cordocentesis carries a higher risk of miscarriage (1%). If maternal infection is confirmed, referral to a fetal medicine specialist for weekly ultrasound and middle cerebral artery (MCA) flow assessments for signs of hydrops and anaemia.[32] MCA Doppler assessment for peak systolic velocity (PSV) is a noninvasive alternative to cord blood sampling. PSV greater than 1.5 MoM indicates severe anaemia and the need for intrauterine transfusion.

Pregnant women contracting the virus in the first half of pregnancy should be counselled that there is no risk of congenital abnormalities, but there is a risk of fetal demise and NIHF.

Varicella-zoster viral infection

Varicella-zoster virus (VZV) causes two clinically distinct forms of disease: varicella (chicken pox) and herpes zoster (shingles). The incidence of varicella infection during pregnancy in the US is estimated to be 1-5/10,000.[36] Primary VZV infection during pregnancy has significant implications and fetal health.[37] If the mother acquires primary VZV infection during the early gestational period (8-20 weeks), the fetus is at risk of developing congenital varicella syndrome although the risk appears to be small (0.4-2%).[37]

Clinical features of congenital varicella syndrome (CVS)[37]:

- cutaneous scars in a dermatomal pattern
- neurological abnormalities (mental retardation, microcephaly, hydrocephalus, seizures & Horner's syndrome)
- ocular abnormalities (optic nerve atrophy, cataracts, chorio-retinitis)
- limb abnormalities (hyploplasia, atrophy, paresis)
- GIT (gastrointestinal reflux and atretic bowel)
- low birth weight

CVS is associated with 30% mortality in the first few months of life and a 15% risk of developing herpes zoster in the first four years of life.[38]

Prenatal diagnosis of CVS s done by PCR testing of fetal blood or amniotic fluid in conjunction with ultrasonography ;for detection of fetal abnormalities.[37]

Neonatal varicella infection

Neonatal varicella infection is a serious illness associated with mortality rate up to 30%.[39] Neonates born to mothers who have clinical disease within five days before to two days after delivery are at the greatest risk for severe disease and poor outcome.[37] This interval allows insufficient time for development of maternal IgG antibodies and passive transfer of antibody protection to the fetus.[39] Clinical presentation is from mild disease like chicken pox in older children to a disseminated disease. Varicella pneumonia, hepatitis, and meningoencephalitis are common manifestation of disseminated neonatal disease. Management includes post exposure prophylaxis with varicella-zoster immune globin to at risk neonates and Acyclovir to neonates with infection.[39] Breastfeeding is encouraged in newborns exposed to or infected with varicella because antibody in breast milk might be protective.[39,40]

Early onset Group B streptococcal (EOGBS) infection of the newborn.

Group B Streptococcus (GBS) is recognised as the most frequent cause of severe early-onset (at least 7 days) infection in newborn infants.[17] GBS is a gram positive bacterium, commonly colonising the gastrointestinal tract and vagina without causing infection. However, it can be an opportunistic pathogen during pregnancy. It has been associated with urinary tract infections, chorioamnionitis, septic abortion, puerperal sepsis and septicaemia.[42]

Pregnant women colonised with GBS during labour can transmit the bacteria to their newborn. Although antenatal treatment for colonization has not been shown to reduce carriage rates for GBS at delivery, intrapartum antibiotic prophylaxis (IAP) is given to reduce the risk of EOGBS.

The incidence of early onset GBS (EOGBS) infection is 0.41/1000 live births in the United Kingdom. In majority of cases the disease is mild.[42] However, about 10% of neonates may develop severe disease with GBS causing pneumonia, meningitis or septicaemia.

The Royal College of Obstetricians and Gynaecologists (RCOG) recommends IAP to be given to at risk pregnant women a previous EOGBS infection, GBS bacteriuria or a positive vaginal swab (only taken for clinical indications) in the current pregnancy and temperature > 38 °C intrapartum.[41]

Some regions like the US, universal screening of all pregnant women between 35 and 37 weeks for GBS with vaginal and rectal swabs is practiced with the exception of at risk group that will receive IAP.[41]

Conclusion

Physicians need to have a high index of suspicion for maternal infections and be equipped with the knowledge on how to manage these conditions. Appropriate counselling of patients about risk of vertical transmission to the fetus is important, follow up plan and referral to a tertiary centre for assessment. Treatment options available to the patients need to be discussed as well. Ideally patients should be informed about different preventative strategies such as vaccinations, avoiding contact with infected people and seeking medical advice should contact occur.

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