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Fetal and Neonatal Infections: Cytomegalo Virus (CMV) Disease

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Abstract

Maternal infection acquired during pregnancy and perinatal period can adversely affect pregnancy outcome as well as morbidity of the newborn. It could result in stillbirth or associated with many congenital anomalies, specific for the type of infection. The organism may be bacterial, viral and protozoal. Early detection and prompt institution of therapy wherever available can prevent morbidity and mortality of the newborn. Vaccination is available against many such infections like varicella, rubella, Hepatitis-B which has helped in reduction of such infection. CMV against which no vaccination is available yet, is emerging as the most common infection in this category. The scope of this article will include an overview of such injections followed by salient features about CMV infection.

Keywords: Intrauterine Infection; Perinatal Infection; Cytomegalovirus.

Introduction

Fetal and neonatal infections could be acquired through [1]:

Congenital infection which are transmitted to the fetus in uterus across placenta or ascending from genital tract; e.g., CMV, Rubella, Toxoplasma, HIV, Parvovirus.

T	Toxoplasmosis
O	Other infections. E.g., -Malaria, Coxsackie B
R	Rubella
C	CMV
H	Herpes simplex, Hepatitis
E	Enteroviruses
S	Syphilis
C	Chicken pox
L	Lyme disease
A	AIDS
P	Parvovirus B 19

Perinatal infection which are predominantly acquired intrapartum, typically during the labor and delivery process through contact with infected blood and secretions during birth; e.g., Herpes simplex, Varicella, Hepatitis B and C.

Postnatal infection if acquired after delivery through the first month of life through breast feeding or direct contact; e.g., Hepatitis A, Respiratory viruses.

The infections may be benign or may lead to still birth or devastating sequele in the baby. The first described intrauterine infection was congenital rubella syndrome.TORCH group signifies Toxoplasmosis, Rubella, Cytomegalo virus (CMV), Herpes simplex virus (HSV) with O standing for other infections [1]. Since then many other infections have been added; the acronym has been expanded to TORCHES CLAP [2].

Epidemiology

The combined overall incidence of TORCH infection is about 0.5 - 2 % of all births. CMV and rubella appear to be commonest. The incidence of HIV is likely to rise in future. Data from ophthalmic units show that CMV and rubella account for 17.8% and 8.4% of congenital cataract respectively. Toxoplasmosis and syphilis are much less frequently seen [3]. Following points are to be kept in mind while suspecting intrauterine infections.

1. Many infections affecting older children and adults are benign in nature but if the host is immune-compromised or if the immune system is not yet fully developed (e.g., neonate), then clinical

manifestations may be quite severe or even fatal. If the same infection is transmitted to the fetus, then the outcome depending on several factors may be benign or quite devastating leading to intrauterine deaths or many sequele (Table-1).

2. Primary infection of the mother carries greater risk of transmission to the fetus as there is no specific antibody in the mother against the organism. In reinfection, protective antibodies produced by previous infections(s) confer immunity to some extent. Similar immunity is also offered by pre-vaccination if available against that organism.
3. Time period in pregnancy during which risk of MTCT is maximum differs from infection to infection; for rubella it is first trimester whereas for toxoplasmosis it is near term gestation. But severity of clinical manifestation is always more, when MTCT occurs in 1st trimester.
4. Not all infected babies, but certain percentage of babies are symptomatic. Similarly not all symptomatic babies but certain percentages have sequele. Sequela is more common in symptomatic babies than the asymptomatic counterpart.
5. Antenatal diagnosis can be made by prenatal ultrasonographic findings, isolation of organism from the amniotic fluid or from fetal blood.
6. Serology- One time TORCH serology is of doubtful utility in the diagnosis of such infection in pregnancy. Ideally the mother should be screened for TORCH serology just before pregnancy or soon after conception, to determine whether she has had any such infection in the past (with presence of high avidity IgG) or she is susceptible to develop them during the course of pregnancy due to lack of any protective IgG antibodies. She needs to be then clearly watched, and followed up for those infections to which she is susceptible. TORCH serology for susceptible infection should be rechecked around 20 weeks gestation or if there are any clinical or ultrasonographic evidences of infection [4]. For confirmation of the diagnosis infection specific better tests (e.g., specific IgM fluorescent antibody) are to be carried out quickly so that therapy if available for the specific infection can be instituted early.
7. Prevention and treatment of infection during pregnancy- If diagnosed, not all infections can be treated; treatment is available for toxoplasmosis, syphilis, HSV and HIV but treatment during first trimester may not be safe. Thus prevention is the golden rule which comprises immunization and protection of pregnant women through improvement in personal hygiene, avoiding contact with urine and oral secretions of others (e.g., CMV). Immunization is available against Rubella, Hepatitis-B and Varicella.

Table 1: Sequaelae following Intrauterine infection [5]

	Overall	Developmental delay	Hearing	Vision	Epilepsy
CMV	47%	66%	67%	3%	6%
Herpes	37%	94%	2%	47%	23%
Rubella	89%	6%	80%	27%	-
Toxoplasmosis	21%	26%	-	82%	11%

Clinical manifestations of intrapartum infection include- IUGR, hepatosplenomegaly, jaundice (conjugated hyperbilirubinemia), pneumonia, petechiae / echymosis, congenital heart disease, microcephaly, encephalitis, intracranial calcification, eye and ear involvement (Table 2). The baby may be normal at birth and manifestations may be delayed for few days to several weeks. Presence of any 3 of the following clinical features suggests possibility of intrauterine infection [4].

i. Maternal history of infection- Painful cervical lymphadenopathy (Rubella, toxoplasmosis), fever, skin rash, infectious mononucleosis like symptoms (CMV), genital herpes, Pleurodynia(Coxsackie-B), high risk sexual behaviour and drug abuse (HIV, Hepatitis- B).
ii. Intrauterine Growth Retardation (IUGR) - CMV (60%), Rubella (60%), Toxoplasmosis (30%). Such babies appear hypoplastic rather than malnourished.
iii. Hepatosplenomegaly- Due to infection or extramedullary hematopoeisis.
iv. Jaundice- Relatively uncommon with Rubella, frequently seen with CMV and Toxoplasmosis. Both conjugated and unconjugated hyperbilirubinemia occur with increase in transaminases.
v. Petechiae and purpura - Thrombocytopenia is common in Rubella and CMV; infrequent with toxoplasmosis.
vi. Meningoencephalitis- Microcephaly (Rubella,

CMV), hydrocephaly (Toxoplamosis), retinopathy, cataract (rubella).

vii. Radiological abnormalities-Intracranial calcifications (Rubella, CMV, Toxoplasmosis), osteochondritis, metaphysitis and periosteal reaction (Syphilis).

viii. Raised IgM in cord blood- Cord blood IgM of > 20 mg/dl suggest fetal infection as IgM is not transferred transplacentally. False positive result may be due to contamination with maternal blood, cross reaction between viruses and presence of rheumatoid factor. False negative result may be due to delayed humoral antibody response on the part of the fetus. The presence of specific IgM fluorescent antibody is diagnostic of specific fetal infection.

Table 2: Clinical Manifestations of Intrauterine Infections [2]

Disease	Abortion	Congenital anomalies	Still birth	IUGR	Preterm birth	Neonatal death	Postnatal disease	Deaf-ness	Ocular problems	Neuro-logical sequelae
Toxopl asma	+		+	+					+	+
Rubella	±	+	+	+						
CMV				+	+	+	+	+	+	+
Herpes						+	+		+	+
Hepatitis-B,C							+			
Entero-virus		±	+							
Syphilis	+	+	+	+	+	+	+	+		+
Chicken pox		+	±	+	+	+	+		+	+
Lyme disease			+	+	±					
AIDS				±			+			
Parvo-virus	+		+							
Malaria			+	+	+					

Cytomegalovirus (CMV) Infection

Epidemiology

(a) CMV is a member of the Herpes virus family and has the largest DNA genome of any virus with lifelong infection. It is found only in human and its name is derived from its histopathologic appearance of infected cells which have abundant cytoplasm and both intranuclear and cytoplasmic inclusions.

(b) CMV is a virus of paradoxes and can be a potential killer or a silent companion lifelong. It is probably one of the most common infections known to humans and is characterized by a self- limiting infections in healthy individuals. In India 80-90% of adults are seropositive. Transmission sources of CMV include saliva, breast milk, cervical and vaginal secretions, urine, semen, blood products, tear, and organ allographs. Its spread requires very close and intimate contact because it is very labile. Indirect transmission is possible via contaminated fomites.

(c) The risk of fetal infection is greatest with maternal primary infection (30%) and negligible with recurrent infection (< 1%). Perinatal sources of transmission are genital tract secretions, saliva and breast milk. Virus is found in breast milk of 96% of sero-positive mothers. Postnatal transmission occurs in 38% of infants which results in symptomatic infections in 50% of very LBW babies; term babies usually remain asymptomatic. Perinatal transmission occurs despite the presence of maternally derived antibodies in the baby [6].

(d) Once the fetus or infant is infected, viral replication occurs primarily in tubular epithelium of the kidneys. After a period of active replication the virus usually becomes latent for lifelong but returns the capability of reactivation under special circumstances. Infected infants may secrete the virus for years in saliva and urine.

Clinical Manifestations

Congenital Infection

Symptomatic congenital infection was originally termed as cytomegalo inclusion disease; 5% have severe form, 5% have mild form and 90% subclinical and chronic infection [6]. Main characteristic signs and symptoms and sequele are given in Table 1 and 2 respectively.

Intracranial calcifications may occur anywhere in the brain but are classically found in periventricular area. Other findings of CNS involvement can include ventricular dilatation, cortical atrophy, chorioretinitis, myelination delay consistent with migrational disorder such as lissencephaly, schizencephaly and pachygyria. All these lead to neurologic dysfunction, developmental abnormalities, deafness and visual problems. Because

Sensory neural hearing loss (SNHL) is the most common sequela of CMV infection (60% in symptomatic and 5% in asymptomatic infants at birth), any infant failing the newborn hearing screen also should be screened for CMV infection. Conversely infants with documented congenital CMV infection should be assessed for hearing loss as neonates and throughout the first year of life [7]. Congenital infections that are symptomatic and severe leading to sequele are more likely to be caused by primary rather than reactivated infections in pregnancy. Asymptomatic congenital CMV infection is likely a leading cause of SNHL [6].

Perinatal Infection

6-12% of seropositive mothers transmit CMV by cervico-vaginal secretions and 40% by breast milk to their infants who usually remain asymptomatic except for occasional pneumonia and sepsis like syndrome and do not exhibit sequele. Premature and ill full term infants may have neurological sequele and psychomotor retardation. However the risk of hearing loss, chorioretinitis and microcephaly does not increase. VLBW babies with transfusion acquired or breast milk acquired infection have a much greater risk of morbidity.

Diagnosis

Prenatal Diagnosis

(1) Infectious mononucleosis like illness in pregnancy– characterized by fatigue, malaise, headache, fever, hepatosplenomegaly and atypical lymphocytosis.

(2) Ultrasonographic evidence of fetal infection viz- oligohydramnios or polyhydramnios, non-immune hydrops, fetal ascites, IUGR, microcephaly, hydrocephalus, periventricular calcifications, pleural or pericardial effusion, hepatosplenomegaly, echogenic bowel or pseudomeconius ileus.

(3) Confirmation by isolation of virus from amniotic fluid (after 22 weeks of gestation) or fetal blood or demonstration of CMV DNA by PCR. Quantitative PCR demonstrating 10 [5] genome equivalents per mL of amniotic fluid is a predictor of symptomatic congenital infection [6].

(4) CMV IgG and IgM- A primary infection is confirmed by seroconversion or simultaneuos detection of IgM and IgG with low functional avidity. For the first weeks after primary infection the functional avidity of IgG is very low rising to a peak in 4-5 month [6].

(5) Interpretation of IgG / IgM antibodies. Negative- < 0.91 U / ml, Equivocal- 0.91-1.1 U / ml, Positive- > 1.1 U / ml.

Postnatal Diagnosis

(1) Infant with characteristic symptoms- IUGR, prematurity, hepatoplenomegaly and jaundice, blueberry muffin like rash reflecting extramedullary hematopoiesis, thrombocy to penia, purpura, microcephaly, periventricular calcifications.

(2) Detection of the characteristic inclusion bodies within desquamated renal epithelial cells so called owl's eye cells in urinary sediments [1].

(3) Detection of CMV PP65 antigen- Positive result confirms; negative result does not rule out infection. Usually used to follow efficacy of therapy [7].

(4) Positive IgG in infant may reflect maternal antibody although a negative result excludes the diagnosis of CMV infection.[6] Demonstration of stable or rising titre in serial specimens during the first year of life cannot confirm congenital infection; it may be due to acquired infection in the first few months of life.

(5) Isolation of virus or demonstration of CMV DNA by PCR from urine or saliva, if detected within 3 weeks of life indicates congenital infection, if negative within 3 weeks of life but positive after 3 weeks, it suggests perinatal infection. CMV is concentrated in high titres in the urine hence a negative viral test from urine in an infant symptomatic for 4 weeks or more does rule out infection, negative blood test cannot rule out [7]. Shell viral cultures are used for better isolation.

Treatment

CMV virus differs from HSV and varicella virus in that it lacks the enzyme thymidine kinase, which renders it resistant to antiviral agents that depend on the enzyme for their action, such as acyclovir. Antiviral therapy should be started if there is CNS involvement or serious end organ disease like hepatitis, pneumonia. Ganciclovir 6mg / kg / dose IV BD for 6 weeks or oral prodrug valganciclovir 16mg / kg / day for 6 weeks is the treatment. Common side effects are (less with valganciclovir) – Neutropenia, thrombocytopenia, testicular atrophy, gonadal tumors. Families should be apprised about the

beneficial and potential harmful effects [6,3].

Prevention

(1) Personal hygiene - Strict personal hygiene includes regular hand wash, avoiding contact with diapers, urine and oral secretions of others and avoiding saliva when kissing a child.

(2) Hyperimmune CMV IVIG antenatally, has been suggested to women with high viral overload and / or detection of low affinity specific CMV IgG [7].

(3) Breast milk - In term infant symptomatic infection through breast milk is rare because of protection by maternally derived CMV IgG and normal antibody in breast milk. Therefore the benefits of breast feeding outweigh the minimal risk of acquired CMV in term babies. However there may be insufficient transplacental IgG to provide adequate protection to preterm infants. Pasteurising breast milk at 220° C or freezing it, will reduce the titre of CMV, but will not eliminate active virus.

(4) Tranfusion products restriction- Use of CMV antibody negative donors, freezing PRBC in glycerol or removing white blood cells through leucocyte filters (since CMV is a leukotropic virus) are strictly to be followed for transfusion to preterm and LBW infants.

Conclusion

(1) Presentation of fetal and neonatal infection are varied and is a differential diagnosis for children with IUGR, Hepatitis, SNHL , vision problem, neurological abnormality and seizures.

(2) Early pregnancy loss is typical of toxoplasmosis. Teratogenic effect is common with CMV, rubella and varicella infection. Rubella, Coxsackie B3 and B4 infections can cause congenital heart disease. Parvovirus infection can cause hydrops fetalis.

(3) Infections which can be treated include toxoplasma, syphilis, herpes & HIV; but treatment during the first trimester is not safe and requires cautionary approach.

(4) Hence prevention of infection during reproductive period gains importance. Vaccination is available for rubella, varicella, Hepatitis B.

(5) Screening can be done for HIV, hepatitis B and C, toxoplasma and CMV.

(6) Asymptomatic children with hearing loss should be screened for CMV infection.

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