Impact of Fetal and Neonatal Viral (and Parasitic) Infections on Later Development and Disease Outcome

Yvonne A. Maldonado

Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA

Abstract

It is estimated that there are 4 million neonatal deaths and an equal number of stillbirths annually, the majority in the developing world. Neonatal deaths account for one third of deaths in children under 5 years of age, and at least one third of neonatal deaths are related to infections. Infections also account for 80% of deaths in the post-neonatal period through 5 years of age. There are several viral and parasitic infections which produce fetal and neonatal morbidity and mortality. Neonatal infections occur during one or more perinatal periods: in utero (congenital), intrapartum (during labor and delivery), and early or late postpartum. Here the term perinatal refers to all of these stages of fetal or neonatal infections. The mechanisms of perinatal viral and parasitic infections vary depending on the specific pathogen, however, all begin with maternal infection. Following maternal infection, organisms may produce indirect placental infection with or without fetal infection, direct fetal or neonatal infection, or primary maternal infection and subsequent perinatal sequelae without either placental or fetal infection. Some pathogens may produce infections by more than one mechanism. This brief report will provide an overview of the pathogenesis, general outcomes, and known pathogens associated with perinatal viral and parasitic infections.

Introduction – The Global Impact of Fetal and Neonatal Infections

It is estimated that there are 4 million neonatal deaths and an equal number of stillbirths annually, the majority in the developing world [1]. Neonatal deaths account for one third of deaths in children under 5 years of age, and at least one third of neonatal deaths are related to infections (fig. 1). Infections also account for 80% of deaths in the post-neonatal period through 5 years of
age. There are several viral and parasitic infections which produce fetal and neonatal morbidity and mortality. This brief report will provide an overview of the pathogenesis, general outcomes, and known pathogens associated with perinatal viral and parasitic infections. It is beyond the scope of this text to discuss diagnosis and treatment.

**Pathogenesis of Fetal and Neonatal Infections**

Neonatal infections occur during one or more perinatal periods: in utero (congenital), intrapartum (during labor and delivery), and early or late postpartum. Here the term perinatal refers to all of these stages of fetal or neonatal infections. The mechanisms of perinatal viral and parasitic infections vary depending on the specific pathogen; however, all begin with maternal infection. Following maternal infection, organisms may produce indirect placental infection with or without fetal infection, direct fetal or neonatal infection, or primary maternal infection and subsequent perinatal sequelae without either placental or fetal infection (fig. 2) [2]. Some pathogens may produce infections by more than one mechanism. The most common viral and parasitic infections affecting the fetus and neonate are outlined in table 1.

The most common mechanism of fetal infection is transplacental passage of the organism after maternal infection and bloodstream invasion, with or without placental infection. Transplacental fetal infection is most commonly seen in congenital infections with cytomegalovirus (CMV), enterovirus, parvovirus, rubella and toxoplasmosis. Transplacental infections with herpes simplex virus (HSV) and varicella zoster virus (VZV) are rare. Intrapartum infections are most commonly seen with human immunodeficiency virus (HIV), HSV, human papillomavirus (HPV), and VZV, and early postpartum infections occur with HIV and are most common with CMV and hepatitis B. Some pathogens cause fetal or neonatal disease secondary only to maternal infection. Severe systemic maternal symptoms with these organisms may lead to abortion, stillbirth or preterm delivery. This is most likely to occur after maternal infections with malaria and [3, 4].

**General Outcomes of Perinatal Viral and Parasitic Infections**

Fetal and neonatal outcomes due to perinatal viral and parasitic infections range from asymptomatic disease to death. These outcomes include embryonic
death and resorption, abortion or stillbirth, prematurity, intrauterine growth retardation, developmental anomalies and teratogenesis, congenital disease, persistent postnatal infection with progressive disease, or asymptomatic infection. The range of outcomes is depicted in table 2.

**Congenital TORCH Infections**

There is a large body of literature regarding the congenital TORCH infections (Toxoplasmosis, Rubella, CMV, HSV, Enterovirus) [5–9]. The overall clinical syndromes and outcomes are summarized in tables 3 and 4.

**Congenital Infections with Other Viruses** [10]

*Hepatitis B*

Hepatitis B is a preventable cause of intrapartum infection, leading to chronic hepatitis B infection in at least 90% of infected neonates [11]. No other congenital symptoms have been identified, although chronically infected individuals have a 25% lifetime likelihood of developing hepatocellular carcinoma. Among infants of hepatitis B-infected mothers, administration of hepatitis B vaccine in the first 12 h of life with concurrent administration of hepatitis B immunoglobulin, followed by additional doses of vaccine at 1–2, 4 and 6 months have 90–95% efficacy in preventing perinatal infection.

---

**Table 1. Viruses and parasites associated with perinatal infections**

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>American trypanosomiasis (Chagas’ disease)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>African trypanosomiasis (African sleeping sickness)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Ascaris</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Giardiasis</td>
</tr>
<tr>
<td>Human herpes virus-6 and -7</td>
<td>Malaria</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Schistosomiasis (bilharziasis)</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Influenza</td>
<td>Trichinosis</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
</tr>
<tr>
<td>Parvovirus</td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td></td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td></td>
</tr>
<tr>
<td>West Nile virus</td>
<td></td>
</tr>
</tbody>
</table>
Human Immunodeficiency Virus

Perinatal HIV infection accounts for over half a million new perinatal infections and over 300,000 pediatric deaths per year [12]. Transmission may occur in utero, intrapartum, and postpartum via breastfeeding. Perinatal HIV infection is uniformly fatal due to progressive immunodeficiency and death secondary to opportunistic infections or organ dysfunction due to primary HIV infection. Approximately 25% of infants born to HIV-infected women will become infected in the absence of preventive antiretroviral therapy. In non-breastfeeding situations, less than 2% of infants will become infected if
prophylactic antiretroviral therapy is administered to infected pregnant women and their infants [13]. Among breastfeeding populations, at least 10% of infants will become infected despite prophylactic antiretroviral therapy [14]. Efforts to prevent breastfeeding transmission are being studied.

Table 3. Clinical manifestations of neonatal ‘TORCH’ infections acquired in utero or at delivery

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Microorganism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rubella virus</td>
</tr>
<tr>
<td></td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td><em>Toxoplasma gondii</em></td>
</tr>
<tr>
<td></td>
<td>herpes simplex virus</td>
</tr>
<tr>
<td></td>
<td>enteroviruses</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>+</td>
</tr>
<tr>
<td>Jaundice</td>
<td>+</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>+</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>+</td>
</tr>
<tr>
<td>Lesions of skin or mucous membranes</td>
<td></td>
</tr>
<tr>
<td>Petechia or purpura</td>
<td>+</td>
</tr>
<tr>
<td>Vesicles</td>
<td>-</td>
</tr>
<tr>
<td>Maculopapular exanthems</td>
<td>-</td>
</tr>
<tr>
<td>Lesions of nervous system</td>
<td></td>
</tr>
<tr>
<td>Meningo encephalitis</td>
<td>+</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>-</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>+</td>
</tr>
<tr>
<td>Intracranial calcifications</td>
<td>-</td>
</tr>
<tr>
<td>Paralysis</td>
<td>-</td>
</tr>
<tr>
<td>Hearing deficits</td>
<td>+</td>
</tr>
<tr>
<td>Lesions of heart</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>+</td>
</tr>
<tr>
<td>Congenital defects</td>
<td>++</td>
</tr>
<tr>
<td>Bone lesions</td>
<td>++</td>
</tr>
<tr>
<td>Eye lesions</td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>++</td>
</tr>
<tr>
<td>Chorioretinitis or retinopathy</td>
<td>++</td>
</tr>
<tr>
<td>Cataracts</td>
<td>++</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>-</td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>+</td>
</tr>
<tr>
<td>Uveitis</td>
<td>-</td>
</tr>
<tr>
<td>Conjunctivitis or keratoconjunctivitis</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– = Either not present or rare in infected infants; + = occurs in infants with infection; ++ = has special diagnostic significance for this infection. Modified from Remington et al. [2], permission pending.</td>
</tr>
</tbody>
</table>
Human Papillomavirus
HPV causes condyloma acuminatum (genital warts) and cervical condylomata. Infants born to a mother with HPV infection may rarely develop juvenile laryngeal papillomatosis, and possibly anogenital warts. Infection of the infant probably occurs by exposure to the virus at delivery, although papillomatosis has been described in infants delivered by cesarean section.

Despite the high prevalence of genital HPV infection, juvenile laryngeal papillomatosis remains a rare disease. The incidence of recurrent respiratory papillomatosis is approximately 3.96 per 100,000 in the pediatric population, with an incidence of 7 of every 1,000 children born to mothers with vaginal condyloma. Treatment of anogenital warts is not optimal, but podophyllum resin or podofilox are often used in older children and adults. Neither has been tested for safety or efficacy in children, and both are contraindicated for use in pregnancy. Laryngeal papillomas recur even after repeated surgical removal. Interferon has been used with some success for treatment of laryngeal papillomas.

Epstein-Barr Virus
Epstein-Barr virus (EBV) is a herpesvirus that causes infectious mononucleosis. Most women of childbearing age have been infected asymptptomatically in childhood. Primary EBV infection during pregnancy is unusual because only 3.0–3.4% of pregnant women are susceptible. Early reports implicated EBV as a cause of congenital anomalies, particularly congenital heart disease. However, there is little evidence suggesting that natal transmission of EBV occurs. EBV

Perinatal Viral and Parasitic Infections

Table 4. Syndromes in the neonate caused by congenital TORCH infections

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Hydrocephalus, diffuse intracranial calcification, chorioretinitis</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Cardiac defects, sensorineural hearing loss, cataracts, microcephaly, ‘blueberry muffin’ skin, lesions, hepatomegaly, interstitial pneumonitis, myocarditis, disturbances in bone growth, intrauterine growth retardation</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Microcephaly, periventricular calcifications, jaundice, petechiae or purpura, hepatosplenomegaly, intrauterine growth retardation</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Skin vessels or scarring, eye scarring, microcephaly or hydranencephaly; vesicular skin rash, keratoconjunctivitis, meningoencephalitis, sepsis with hepatic failure</td>
</tr>
</tbody>
</table>

Modified from Remington et al. [2], permission pending.
can be transmitted to newborns in the perinatal period by blood transfusion. There is no evidence at present that EBV causes congenital anomalies.

**Human Herpesviruses**

Human herpesvirus (HHV)-6 has been identified as a cause of exanthema subitum (roseola). HHV-6 is ubiquitous in the human population regardless of geographic area and infects more than 90% of infants during the first year of life. The usual route of transmission is perinatal or postnatal. No cases of symptomatic intrauterine HHV-6 infection have been confirmed since the agent was identified in 1986, although there is evidence of asymptomatic intrauterine infection. Evidence of re-infection after presumed congenital HHV-6 infection has also been demonstrated. As diagnostic assays become more widely available, congenital infections may be recognized. However, primary HHV-6 infection should be rare during pregnancy because almost all adult women have been infected in childhood.

In addition to roseola, postnatal HHV-6 infection may cause acute, nonspecific febrile illnesses in infants. Other associations among infants include fulminant hepatitis, a mononucleosis-like syndrome, and pneumonitis.

HHV-7 was discovered in 1990. It belongs to the Roseolovirus genus within the Betaherpesviririnae subfamily, along with HHV-6 and CMV. Like HHV-6, it is ubiquitous and causes primary infection during childhood. Symptomatic infection with HHV-7 appears to be less common than with HHV-6. The primary mechanism of transmission is from contact with saliva of infected individuals. Since HHV-7 DNA has been detected in breast milk, breastfeeding may be another source of infection. Pregnancy may be associated with reactivation of HHV-7. However, perinatal transmission from contact with infected maternal secretions is unknown, and neonatal infections with HHV-7 have not been reported. Clinical symptoms are rarely associated with HHV-7 infection, but include nonspecific fever, with or without rash. Clinically apparent HHV-7 infections appear to have a high rate of central nervous system involvement.

**Influenza**

Population-based epidemiologic studies have not demonstrated that influenza infections during pregnancy are associated with adverse perinatal outcomes. However, influenza infections during pregnancy are more likely to result in hospitalization than for nonpregnant adults. Intrauterine exposure to influenza virus does not cause a consistent syndrome. A number of studies have investigated the possible association between influenza infection in pregnant women and subsequent development of bipolar affective disorders or schizophrenia among their offspring, with mixed results. Infections acquired by infants in the neonatal period are not uncommon and may be fatal. Several outbreaks of influenza virus infection have occurred in neonatal intensive care units. In general, illness has been mild.
Pregnancy is not a contraindication for the administration of influenza vaccine.

**Mumps**
Congenital anomalies have not been associated with mumps infection during pregnancy, however, spontaneous abortion after mumps infection during the first trimester of pregnancy is increased. Mumps infection during pregnancy may be associated with development of endocardial fibroelastosis in offspring. Parotid swelling and pneumonia in perinatal mumps infection has been reported.

**Parvovirus B19**
Parvovirus B19, the cause of erythema infectiosum (fifth disease), is a known cause of congenital infection which may result in miscarriage, fetal hydrops and fetal anemia. The risk of transplacental fetal infection and fetal loss are 30 and 9%, respectively. Fetal loss occurs most often in the early second trimester. Parvovirus is associated with up to 20% of nonimmune fetal hydrops. Diagnosis of fetal infection can be based on the detection of virus in amniotic fluid and placental tissue. No treatment or vaccine is available, but intrauterine blood transfusion may prevent fetal loss.

**Respiratory Syncytial Virus**
There is no evidence that respiratory syncytial virus (RSV) causes intrauterine infection. Maternal infection has no known adverse effect on the fetus.

RSV infections are frequently acquired by infants and are associated with a high mortality rate. Two thirds of all infants will be infected with RSV in the first year of life, one third will develop lower respiratory tract symptoms, 2.5% will be hospitalized, and 1 in 1,000 infants will die [15]. Infection with RSV in infants younger than 4 weeks may be asymptomatic, consist of an afebrile upper respiratory syndrome, or be accompanied by fever, bronchiolitis or pneumonia, and apnea. Deaths occur most frequently in infants with underlying cardiac or respiratory conditions. Premature infants with bronchopulmonary dysplasia are especially likely to develop severe infections.

There is a lack of consensus regarding the use of aerosolized ribavirin in infants with RSV infection. No clear improvement in clinical outcomes is consistent across studies of both ventilated and nonventilated infants with RSV infection. However, there is clear evidence for the benefit of prophylaxis against RSV infection in infants at high risk for complications. A humanized anti-RSV monoclonal antibody preparation, palivizumab, is the preferred method of RSV prophylaxis.

**Lymphocytic Choriomeningitis Virus**
Lymphocytic choriomeningitis virus (LCV) is spread from animals, primarily rodents, to humans. Person-to-person spread has not been described.
Mice and hamsters are most often implicated as the source of human infections.

LCV infections during pregnancy may be underdiagnosed as causes of congenital infections, and are associated with abortion, intrauterine infection, and perinatal infection. Intrauterine infection of the fetus results in congenital hydrocephalus and chorioretinitis. Other problems include severe hyperbilirubinemia and myopia.

Because apparently healthy mice and hamsters may shed LCV chronically, pregnant women should avoid direct contact with these animals as well as with aerosolized excreta. LCV causes spontaneous abortions. Hydrocephalus and chorioretinitis are common in infants who survive intrauterine infection. Women who acquire an LCV infection during the weeks immediately before delivery may transmit the virus to their infants. Although the total number of intrauterine and perinatal infections from LCV is not large, the incidence of serious sequelae in the infant appears to be high.

**West Nile Virus**

West Nile virus (WNV) is a mosquito-borne flavivirus that has caused epidemic infections in the United States since its introduction in 1999. Since then, 3 cases of intrauterine and breastfeeding transmission have been reported. While spontaneous abortion and stillbirth have been associated with flavivirus infections, these viruses have not previously been reported to be teratogenic. During 2002, the Centers for Disease Control and Prevention investigated 3 other cases of maternal WNV infection in which the infants were all born at full term with no evidence of WNV infection or congenital sequelae.

**Varicella Zoster Virus**

VZV is a rare but serious cause of congenital infection associated with fetal death or severe embryopathy [16]. The risk of congenital infection is 1–2%, occurring almost exclusively in the first 20 weeks of gestation. VZV is more commonly associated with intrapartum or early postpartum infection which may produce severe or fatal disseminated disease in the neonate. These infants should be treated with intravenous immunoglobulin (IVIG) or VariZIG if that is available, in addition to intravenous acyclovir. Infants with perinatal VZV infection are at risk for early development of zoster.

**Congenital Infections with Other Parasites [17]**

Parasitic infections are highly prevalent in most of the world. The placenta serves as an effective barrier, even in infections with malaria and schistosomiasis in which systemic involvement and hematogenous spread are common. Although transplacental infections of the fetus are uncommon, in developing
countries the prevalence of parasitic infections among infants younger than 1 month of age is high, primarily through transmission during or shortly after birth.

Ascaris lumbricoides

Ascaris lumbricoides is the most prevalent parasitic infection worldwide, affecting up to 1 billion people. Because Ascaris may migrate to many organs, worms are occasionally found in the uterus and the fallopian tubes. Fetuses are apparently able to mount an immune response to maternal Ascaris infection, but congenital infections are extremely rare and appear to be benign. Investigators have reported fetal evidence of Ascaris infection in infants as early as 1 week of age and in one infant with failure to thrive and bloody diarrhea at 3 weeks of age who responded to levamisole therapy.

Giardia lamblia

Giardia lamblia causes a localized intestinal infection, with no systemic involvement. Hence, *G. lamblia* infection in pregnancy is not associated with fetal infection. Severe maternal infection that compromises nutrition could affect fetal growth, but such severe illness is rare. Neonatal *G. lamblia* infection can result from fecal contamination at birth. Infected infants are usually asymptomatic. Treatment of pregnant women with giardiasis is generally deferred until after the first trimester.

Trypanosoma cruzi

Millions of people in Central and South America are infected by *Trypanosoma cruzi* (American trypanosomiasis, Chagas’ disease). Because of the chronicity of these infections, they have a significant impact on public health.

*T. cruzi* is transmitted by the bite of an infected vector, the cone-nosed bug. Infections can also be acquired by blood transfusion and transplacentally. Most congenital infections occur in infants born to women with the chronic form of the disease despite the fact that the mother is asymptomatic. Congenital infections occur in 1–4% of women with serologic evidence of Chagas’ disease. Congenitally infected infants may develop symptoms at birth or during the first few weeks of life. Early-onset jaundice, anemia, and petechiae are common. Infected infants may have hepatosplenomegaly, cardiomegaly, and congestive heart failure, as well as involvement of the esophagus leading to dysphagia, regurgitation, and megaesophagus. Some infants have myxedematous edema. Pneumonitis has been associated with infection of the amnionic epithelium. Congenitally infected infants can be born with encephalitis or develop it postnatally. The cerebrospinal fluid shows mild lymphocytic pleocytosis. Cataracts and opacification of the media of the eye have been observed. Less than half of congenitally infected infants survive past 2 years of age. Of those who survive for 2 years or longer, 74% have no
serious clinical symptoms despite continued parasitemia. However, subclinical abnormalities may persist. Congenital infections can recur during subsequent pregnancies. The same mother, however, often has healthy children both before and after the affected one.

Trypanosoma brucei gambiense and T. brucei rhodesiense

Few cases of congenital infection with Trypanosoma brucei gambiense and T. brucei rhodesiense (African trypanosomiasis – African sleeping sickness) have been reported. However, congenital infection is most likely underreported. Humans are infected by the bite of an infected tsetse fly. The parasite can be transmitted transplacentally. Transplacental infection can cause prematurity, abortion, and stillbirth. Central nervous system involvement is common in congenital infection and in some infants may be slowly progressive.

The diagnosis should be suspected in an infant with unexplained fever, anemia, hepatosplenomegaly, or progressive neurologic symptoms whose mother is from an endemic area. The parasite can be identified in thick smears from peripheral blood or in the cerebrospinal fluid. In infants, treatment with suramin or melarsoprol has been reported with good results.

Entamoeba histolytica

Entamoeba histolytica infection during pregnancy may be more severe and have a higher fatality rate than in nonpregnant women. Amebiasis has been reported in infants as young as 3–6 weeks of age. In most instances, person-to-person transmission is likely with the mother as the probable source of the infant’s infection. Perinatal infections have occurred in countries such as the United States in which the disease is rare.

Most infants reported with amebiasis had severe illness, with bloody diarrhea, sometimes followed by development of hepatomegaly and hepatic abscess, rectal abscess, and gangrene of the appendix and colon with perforation and peritonitis. Maternal amebiasis has also been associated with low birthweight. Infants have been successfully treated with oral metronidazole. Critically ill children should receive intravenous therapy with dehydroemetine or metronidazole.

Malaria

Malaria is a major global health problem, and its impact on pregnancy and infant mortality has been underestimated. Up to 40% of the world’s pregnant women are infected with malaria during pregnancy, and it is estimated that annually 75,000–200,000 infant deaths are associated with malaria infection in pregnancy. Those with little or no preexisting malaria immunity have an increased risk of maternal and perinatal mortality. Fetal and perinatal loss may be as high as 60–70% in nonimmune women with malaria. Both the density and the prevalence of parasitemia are increased in pregnant women.

236
compared with women who are not pregnant. The prevalence as well as the
density of the parasitemia decreases with increasing parity. Malaria infects
the placenta as well as the fetus. Low birthweight is more common when the
placenta is infected by parasites than when the mother is infected but the pla-
centa is not. Both maternal anemia and placental insufficiency affect the
fetus. Infants who have parasites demonstrable in their cord blood appear to
be more severely affected than those who do not have parasitemia at the time
of delivery. Studies of the effect of malaria on anemia, low birthweight, and
infant mortality in malaria-endemic areas reveal that 3–15% of anemia,
8–14% of low birthweight, 8–36% of preterm low birthweight, 13–70% of
intrauterine growth retardation and low birthweight, and 3–8% of infant mor-
tality are attributable to malaria. Maternal anemia is associated with low
birthweight, and fetal anemia is associated with increased infant mortality.
Malaria therefore contributes to fetal loss, stillbirth, prematurity, and neo-
aternal death.

Common clinical findings in congenital malaria are fever, anemia, and
splenomegaly, present in more than 80% of cases. Anemia is associated with
reticulocytosis in about half the cases. Jaundice and hyperbilirubinemia are
found in about a third of cases. Either direct or indirect bilirubin may be ele-
vated, depending on whether liver dysfunction or hemolysis is the most
important process in an individual case. Hepatomegaly may also be present
but is less common than splenomegaly. Nonspecific findings include failure to
thrive, poor feeding, regurgitation, and loose stools. In developing countries,
when malaria occurs during the first few months of life, it is frequently com-
plicated by other illness, such as pneumonia, septicemia, and diarrhea.

Chloroquine alone has been beneficial when used as prophylaxis during
pregnancy. Despite widespread use of weekly doses of chloroquine in preg-
nant women, teratogenic effects have not been confirmed in controlled trials.

Schistosomiasis
Schistosomiasis contributes to infertility by causing sclerosis of the fallop-
ian tubes or cervix. It is estimated that 9–13 million women may be afflicted
by genital schistosomiasis in Africa alone. The placenta usually does not
become infected until the 3rd month of pregnancy or thereafter. Placental
infection is as high as 25% in endemic areas, but the infestations are mild, and
there is little evidence that the size or weight of the infant is affected. Placental
bilharziasis is not an important cause of intrauterine growth retar-
dation or prematurity.

Trichinosis
Prenatal transmission of trichinosis from mother to infant is rare. Despite
this, *Trichinella spiralis* has been found in the placenta and the milk of
nursing women as well as in mammary gland tissue, and can be passed to the
infant via breast milk.
References


Discussion

Dr. Ogra: You have very elegantly outlined the spectrum of infectious agents to which the fetus and the neonate are constantly exposed. It may not be a small number of organisms, and at the moment we may only be looking at the tip of the iceberg. Yet very few of them seem to produce significant disease in the fetal and newborn period. Do you have any thoughts on how important the placenta may be as a determinant of transmission of the infectious agents from the mother to the child? The ability of the fetus to mount an immune response at a given time may also determine the outcome of these fetal infections. Is there any information relative to the tropism of fetal tissues
to different organisms to produce specific disease? We know, for example, that poliomyelitis is not seen in fetal life as can be seen with other infections such as CMV, HSV, rubella, etc. Why don't we find fetal disease with all agents to which a susceptible mother may be exposed?

Are there any specific windows of programming for the development of subsequent disease outcome? I am not talking about hearing loss with CMV, but about something like the development of cancer with chronic hepatitis or the development of neurological disease with toxoplasmosis or heart disease with chlamydia. Are there any specific windows which we might be able to identify for this age group which could be focused on for future investigative effort?

Dr. Maldonado: Dr. Wilson and Dr. Arvin in my group have looked at HSV and CMV over the years, specifically at maternal but less at fetal responses. Clearly there is evidence that the fetus can to some degree mount immune responses to these organisms. However, the vast majority of the information really points to the maternal response as being the primary mechanism of prevention of disease in the infant, and most of the studies are epidemiologic as well as directly case-based. In the cohorts of women who are infected with particularly CMV or HSV, for which the group at Seattle is quite well known, the epidemiologic studies clearly show that women with predisposing immunity are much less likely to have infants with infection. We do know, of course, that the placenta plays quite an important role, and again as far as I can tell there haven't been studies comparing the roles of placental involvement versus maternal immunity in quite the depth that I would like, but maternal immunity plays quite an important role for the majority of these. Now having said that, there are organisms such as toxoplasmosis, enterovirus, some of the parasitic infections, malaria in particular, where immunity is important but does not guarantee the absence of infection in subsequent pregnancies, whereas that tends not to be the case for herpes or CMV disease. So clearly there are differential responses. The argument for placental disease and placental protection is an important one which is very difficult to assess. There are very poor data looking at that and at this point most of those are hypothetically based on animal studies. One of the prime examples of how the placenta can be effective is the absence of the placental involvement with HIV disease. With HIV infection there may be cell-free HIV that crosses the placenta, but primarily it is related to CD4-infected cells which cross the placenta, and the fact that the immune system is impaired really leads one to understand that those cells, in the absence of HIV and other infections, do not produce disease whereas since the target, the affected cell, is also the infected cell, the effect of losing the placental barrier results in about 20–25% affect of transmission.

Your final question about windows of opportunities; I think this will really vary depending on the disease. For instance, there have been efforts to develop vaccines which were quite unsuccessful in the past; in fact currently a circumsporozoite vaccine for malaria is being studied at a number of sites, and HSV and CMV vaccines have also been studied. Clearly the time to intervene would be before the reproductive age. HPV vaccine is for other reasons, not because of fetal and neonatal infection, best given in the pre-reproductive time. Rubella vaccine is another example of a vaccine that can be given at a time when immunity really prevents infection that would occur 15–20 years down the line. So the windows of opportunities for vaccinations are quite important. However, possibly because of latency and possibly because of poor efforts, and the lack of effect of immunogenicity on disease outcome, these viruses have been quite difficult.

Dr. Scholl: I have a question about breastfeeding by HIV-positive women. There is quite large transmission even when the mother is using antiretroviral therapy. Has anyone tried simple interventions such as heating the breast milk?
Dr. Maldonado: First, there are a number of studies that clearly demonstrate very low HIV transmission rates if pregnant women are treated with a highly active three drug regimen. Regarding heating of breast milk, yes, that has been done. Super heating is one of the areas that has been looked at. In fact it was part of the NIH master plan and we tried to prioritize what kind of strategies we can use outside the USA, primarily because in the USA most women don’t need to breastfeed if they are infected. There is an easy way to super heat the milk even in the home, but the problem is that it is very difficult to even provide formula in many situations. So yes it is possible to heat breast milk, but in the developing world that it is not something that is easy to get into the community. The other issue is stigma; if a woman doesn’t breastfeeding people know why she isn’t breastfeeding. The WHO in their statement on changing breastfeeding practices through 6 months gave a very important signal to these women that it is alright to actually stop after 6 months. So that is a very good point that may not be able to be translated into reality.

Dr. Prentice: In relation to this issue there is a very exciting paper in the Lancet by Coovadia et al. [1] from Kwazulu Natal which really shows some very different numbers and is obviously going to reignite this whole debate, and I think it is already doing so. The 3- to 6-month risk for exclusive breastfeeding was actually only 4% and that was increased 11-fold by the introduction of replacement feeding. The mortality of exclusively breastfed children was 6% compared to the 15% of those receiving replacement feeds. So it is very much in the same direction of the other data but somewhat stronger.

Dr. Maldonado: We were talking about what to do next and it is really unclear. The issue is that the data strongly suggest that replacement feeding is not a panacea; after 6 months the risk of mortality among non-breastfed, non-HIV-infected babies is low, but it is not zero. The issue is that in the most recently done trials the risks are higher than anticipated and the transmission rates are still high. The other issue is that only about 30% of women around the world really exclusively breastfeed even in the first 3–4 weeks of life, and it is very difficult to promote exclusive breastfeeding all the way through 6 months. Although not proven, studies have suggested that exclusive breastfeeding may be better and actually the transmission rates of HIV may be higher among mixed breast-feeding babies, especially when solids are introduced before the first 6 months of life. At this point we are rethinking ways to come up with a replacement feeding which may help. Of course micronutrient supplementation does not seem to make a difference either.

Dr. Walker: As we all know the first 2 months of breastfeeding is probably the most important time because the most protective factors are delivered then. If breast milk is super heated, then nearly all the protective factors are killed. How extensively has antiretroviral treatment been studied in conjunction with breastfeeding compared to non-breastfeeding in terms of morbidity? Has that been looked at because this is a fairly new phenomenon? We don’t really know whether antiretroviral treatment during breastfeeding is less or more dangerous than if the baby didn’t get the breast milk.

Dr. Maldonado: It took us about 5 years to go from our phase 1 trial of infant antiretroviral therapy plus breast feeding to our phase 3 trial because of FDA issues and getting the study approved in the USA. We did our phase 1 trial in 75 mother–infant pairs in Zimbabwe several years ago. The numbers were quite small and the regimen was very safe, and there was some transmission but again statistically not significant. There were 2 infected infants out of 75 who were breastfed and received nevirapine. The current study of 1,500 mother–infant pairs is powered to look at about a 25% reduction in transmission. Other alternatives would be to try to vaccinate the infants with the canary pox vaccine which is undergoing phase 1 trials now in Uganda.
Dr. Martinez Cabruja: In the tropics there is an endemic viral infection called dengue which is transmitted by a mosquito. Do you have any data about the effect of dengue infection on the fetus during the first trimester of pregnancy?

Dr. Maldonado: There is not a lot of prospective data but the suggestion is that severe dengue actually works much more like malaria, like measles than influenza. The effect is primarily on the maternal side and will lead frequently to stillbirth or to early embryonic resorption. To my knowledge there is no evidence of PCR-based identification of the virus on the fetal side.

Dr. Abdelmoez: What is the mechanism of neonatal bilharzial infection, schistosomiasis?

Dr. Maldonado: Schistosomiasis affects the placenta. There is infection of the placenta and it affects the fetus in that respect. Actually schistosomes can be found in placental pathology in the small studies that have been done. Primarily there can be placentitis and then secondarily schistosomes will be identified in the fetal liver. There are very few studies looking at the pathology in the fetus.

Dr. Kumara: Your data show that the incidence of HIV, using AZT and 3TC, is 14.9% compared to breastfeeding which is only 1.9%. This causes me some concern because we use AZT and 3TC according to the WHO recommendations but without breastfeeding. What is your opinion?

Dr. Maldonado: The issue is about the effect of antiretroviral therapy on HIV transmission and unfortunately there are different standards of therapy depending on what part of the world you live in. The WHO is very clear that the preferred regimen worldwide is AZT plus a single dose of nevirapine to the mother and the infant within the first 72 h of life. However, in the USA and the developed world the standard is the zidovudine treatment which begins in the second trimester of life as oral therapy, intravenous therapy during labor and delivery, and then 6 months of oral therapy to the infant after delivery. That is the recommended regimen, but in practice in the developed world most infected women, if they have access to care, will be receiving the triple therapy which in fact resulted in that 1.6% transmission rate. Using the AZT regimen only results in a two-thirds reduction. Although that is quite large it reduces the transmission from 25 to 8%; using the triple therapy in the women along with the AZT backbone results in an about 1–2% transmission rate, and using the WHO recommendations will probably result in something in the order an 8–10% transmission rate without breastfeeding, with breastfeeding you might add another 5% to that.

Dr. Kumara: Are your data without or with breastfeeding?

Dr. Maldonado: Without breast feeding, no breast feeding.

Dr. Wilson: The bottom line is that nevirapine is certainly not the ideal form of therapy for the trial you are looking at; it is very clear that the decision to use nevirapine is based on reasons other than efficacy. Now the real world reality is the real world reality, but this begins to smack of the problem that the WHO created with multidrug-resistant, now extremely drug-resistant TB, where they stuck with recommending a regimen that we knew was likely to fail. If in fact the goal is to drop the HIV prevalence in the world to as low as we possibly can in order to try to do something real against this epidemic, why are we doing things that we know are inadequate?

Dr. Maldonado: We have been trying to start this study for 6 years instead of doing the simpler generic triple study earlier on. The point is that originally when we first began these trials outside the USA, AZT treatment first had an unacceptable reduction of two thirds and we knew that HAART (triple antiretroviral therapy) therapy could reduce even more. But at the time triple therapy number one was quite expensive, it involved 3 different very expensive drugs that are given individually. As we know today those 3 drugs are now available in one pill, and more importantly as of 3 or 4 years ago those 3 drugs could be bought in a generic form for much less.
Unfortunately through the NIH system we were not allowed to use generic drugs in any of our trials. It was only about 3 years ago that we were allowed to do that, which is why we have been able to go forward with this trial. Even though the drug was being provided free of charge to us, the idea that we would move forward with the generic treatment was unacceptable. So we went through many proposed regimens before we set down one that would be acceptable to the funding agencies.

Dr. Wilson: But I think the question was right on: why is the WHO recommending a regimen that we know is inferior?

Dr. Maldonado: Another major concern is about long-term toxicity, primarily in the form of resistance in the mother who will receive one dose but may receive more than one dose if she has multiple infants, and potentially in the infant too. We are trying now to alter these trials. In fact there is presently a trial in South Africa using triple therapy but it is funded by different mechanisms and probably not powered the same way to answer the question properly. Probably the best practices will lag behind what is available by about 3–5 years at least. So currently if we were able to, we would be doing a triple therapy generic trial.

Dr. Kumara: I have additional questions that I think also need Dr. Walker's comments. What possibly happens with the microbiota of the neonates born vaginally to mothers with those infections?

Dr. Maldonado: What happens to the infants of the women who die? We don't know. That is again an operational question, and most of us who are involved with these studies actually spend a lot of the time not doing scientific trials but setting up community-based programs to sustain our programming for the women rather than doing clinical interventions. Many of us bring in funding to provide prenatal care, to find homes for the children, and those are additional costs that we seek funding for. We do a lot of community-based work, and governments and NGOs have been very useful for us in that situation. In sub-Saharan Africa the foreign donors have been quite helpful. In Asia the NGOs have received quite a bit of funding, not enough, but funding to support the care of those infants.

References