Intrauterine Fetal Infections: Do-Able Approaches

Vatsala Dadwal¹ · Reema Kumar Bhatt²

Published online: 25 March 2020
© Society of Fetal Medicine 2020

Introduction

Infections in pregnancy pose a management dilemma, as treatment is targeted towards two patients, the infected woman and the developing fetus. The issues to consider are the risk of transmission to the fetus, diagnosis of fetal infection, interventions to possibly prevent/treat fetal infections in utero, diagnosis of infection in the newborn and eventually, postnatal management of the newborn. The infected newborn infant may be normal or may show abnormal growth, malformations, neurological developmental delay and long-term consequences or multiple clinical and laboratory abnormalities.

Scenarios specific to a particular infectious agent have been put together in this issue of the Journal of Fetal Medicine by a panel of expert practitioners, and it is hoped that this compendium will serve as a ready reference for the practitioner and expert alike. This section places a different perspective and works backwards from clinical presentation to do-able management.

Infections with risk of perinatal transmission include syphilis, varicella, rubella, cytomegalovirus (CMV), toxoplasmosis, parvovirus and human immunodeficiency virus (HIV). These infections may have short-term and long-term repercussions. Many congenital infections are asymptomatic at birth. Some congenital infections can be

successfully prevented provided adequate strategies are implemented in a timely manner.

For effectively managing perinatal infections, there is a need for clarity on several issues, not only for taking decisions but also for adequate counseling:

- (1) What is the percentage of pregnant patients that can be expected to acquire a disease?
- (2) How frequently does vertical transmission happen to the fetus?
- (3) In which trimester is the affection greatest?
- (4) With what frequency does this affection seriously and permanently affect the fetus?
- (5) How can we diagnose that the fetus is infected?
- (6) Is there some way of preventing perinatal affection or treating in utero?

Intrauterine infections of the fetus may occur by several routes. The most probable route of intrauterine infection during pregnancy is transplacental passage. Organisms acquired by the transplacental route reach the fetal blood supply and are subsequently filtered by the fetal liver and spleen. Therefore, the discovery of organisms in the fetal liver or spleen at autopsy can be used as evidence of perinatally acquired infection. A live-born infant infected hematogenously may show evidence of septicemia, meningitis, or infection of the heart, adrenal gland, liver, or spleen. Infection may also result from fetal aspiration of amniotic fluid that has become contaminated following migration of organisms through the fetal membranes or following infection of decidual tissues and contiguous placental villi. The risk of sequelae of infection increases not only for the fetus but also for the mother as the time following rupture of membranes increases.

✉ Reema Kumar Bhatt
reemakamalbhatt@yahoo.co

Vatsala Dadwal
vatslad@hotmail.com

¹ AIIMS, New Delhi, Delhi, India

² Army Hospital Research and Referral, New Delhi, Delhi, India

Effects on the Fetus

Fetal infection due to vertical transmission can have a varied impact on the fetus. It may result in delivery of a normal infant or can result in miscarriage, stillbirth, prematurity, low birth weight, developmental abnormalities, congenital disease, and/or persistent neonatal infection.

Miscarriages and Stillbirth

Maternal infections caused by most organisms that can cross the placenta including rubella, syphilis, toxoplasmosis, cytomegalovirus, and herpes simplex virus may result in miscarriages or stillbirth. However, it needs to be emphasized that fetal infections are not a cause of recurrent pregnancy loss.

Fetal Growth Restriction

Early onset (< 24 weeks), severe (< 5th percentile), symmetrical fetal growth restriction and/or associated sonographic markers like echogenicity and calcification of the brain and/or liver and hydrops indicating fetal infection with cytomegalovirus, toxoplasmosis, rubella and varicella warrant specific PCR testing on amniotic fluid, in case the mother is infected based on serology and avidity testing. Maternal rubella infection has also been shown to result in small-for-date infants. The mechanism for this appears to be related most directly to viral inhibition of cell multiplication by interference with mitotic activity. The virus also causes an obliterative angiopathy of small blood vessels and capillaries and with persistent infection, progressive damage to the placental vasculature takes place.

Structural Anomalies

Rubella and cytomegalovirus have been conclusively shown to behave as teratogens in the fetus. Congenital infection may affect any system. Anomalies include central nervous system and cardiovascular abnormalities, deafness and mental retardation. In addition, cataracts are associated with rubella and chorioretinitis is associated with cytomegalovirus infections. The period of gestation is pivotal to the impact it creates on the fetus. Rubella has no impact if contracted in the third trimester and congenital syphilis may be prevented if the mother is treated before the 16th week of pregnancy.

Persistent Postnatal Infection

Rubella virus, cytomegalovirus, herpes simplex virus, varicella-herpes zoster virus and *Toxoplasma gondii* have

been shown to survive in (and may be isolated from) infants for remains not just for months but years after birth. The persistence of these organisms may result in disease and the mechanisms by which some infants resist the consequences of infection and others do not is incompletely understood.

Diagnosis

There is increasing awareness about the impact of fetal infections and this has stoked the need for updating diagnostic techniques for in utero infections. Fetal sonographic findings and serology to identify specific infectious agent are conventionally used to arrive at a prenatal diagnosis of fetal manifestations of infections. Traditionally, the mainstay for diagnosis of fetal infections is detection of microorganisms by cultures, immunologic methods and special molecular biology techniques. The manifestations of fetal infection can be direct like fetal malformation and/or fetal death that would have occurred by the time infection is confirmed by culture or other histopathological methods or indirect like intrauterine growth restriction or calcification of fetal organs.

Ultrasound is a useful modality in detection of almost all fetal anomalies that are typical of a fetal infection and is considered the safest, least invasive and effective way for detection and monitoring of antenatal infections. Ultrasound may show some nonspecific findings suggestive of congenital infections such as fetal growth restriction, ventriculomegaly or intracranial calcifications that needs further investigation for confirmation. Also, response to therapy is judged by ultrasound in infections such as parvovirus to assess resolution of hydrops. 3D ultrasound improves detection of fetal anomalies like cleft lip, brain lesions, limb malformations and structural heart defects associated with fetal infections. Thus, the use of ultrasound to detect markers of infection will help the clinicians to accurately identify the causative agent, correlate with antepartum and postpartum syndrome associated with it and aid in reducing the problem of adverse outcome which can happen with an unsuspected or undiagnosed fetal infection.

An essential common step is to confirm maternal infection, most frequently serologically, by testing for pathogen-specific IgG and IgM. The interpretation of results can be difficult, particularly in the absence of a premorbid sample, such that seroconversion from IgG negative to IgG positive cannot be demonstrated. Here comes the role of looking for four-fold increase in titre of IgG and avidity testing where low avidity is a pointer to recent infection and high avidity gives assurance of old infection. The risk of transmission to the fetus and the

chance of fetal damage relate specifically to the pathogen and gestation at infection. Amniocentesis to test for the presence of RNA or DNA by PCR is the mainstay of diagnosis of fetal infection in most cases but the timing of the test in relation to the likely point at which transmission occurred is crucial. Fetal infection is documented by amniotic fluid culture or PCR and PCR sensitivity approaches 100% in gestations > 21 weeks.

The detection of virus alone is not synonymous with fetal damage and a negative result does not completely exclude the possibility of fetal infection. Ultrasound surveillance is the primary tool for determining the degree of damage but it, too, has limitations in accurately predicting the outcome. There are a few therapeutic options for the infected fetus and these are currently limited to intrauterine blood transfusion in cases of anemia due to parvovirus infection. Transplacental therapy for syphilis, ARV for prevention of mother to child transmission of HIV are currently practiced.

Screening in Antenatal period

Screening is mandatory for certain infections since maternal to child transmission can be prevented and treated effectively.

Screening for syphilis in pregnancy is mandatory to identify women with active syphilis to offer treatment of their own infection. Rubella IgG screening should be part of antenatal protocol. In suspected cases of rubella, the IgG and IgM titer should be measured even if the patient was previous positive for rubella IgG.

Universal free serological testing for Hepatitis B Virus should be offered to all pregnant women on an opt out basis so that effective postnatal intervention can be offered to infected women to decrease the risk of MCT.

Both the American College of Obstetricians and Gynecologists (ACOG) and the CDC recommend an “opt out” approach to ensure routine HIV screening for all pregnant women, ideally performed at the first prenatal visit. There is also a recommendation by CDC for repeat testing in the third trimester, citing its cost effectiveness even in areas of low prevalence.

The screening for other infections needs to be done on the basis of clinical suspicion and exposure only.

In Utero Treatment

In cases of suspected fetal infection, clinicians need to be familiar with the risk and spectrum of associated fetal damage, the benefits and limitations of prenatal diagnosis and the effectiveness of potential treatment in order to determine an appropriate management plan. Two strategies

need consideration: prevention of transmission of infection or in utero treatment.

Treatment for Prevention of Infection in Fetus

Treatment of the mother can in certain conditions prevent vertical transmission to the fetus.

In case of Toxoplasmosis, spiramycin administered to the mother reduces the risk of fetal infection by 60–70%. Where primary maternal infection is confirmed before 16 weeks of gestation empirical treatment must be started prior to amniocentesis, as the longer the interval between maternal seroconversion and the start of treatment, the greater the likelihood of fetal transmission.

Provision of immunoprophylaxis for infants born to infected mothers, including hepatitis B vaccine and hepatitis B immune globulin within 12 h of birth should be done. There is a role of screening all HBsAg positive women for HBV DNA to guide the use of antiviral therapy when HBV DNA is > 200,000 IU/ml.

Early Highly Active Antiretroviral Therapy (HAART) has made a paradigm change in preventing perinatal HIV transmission.

The varicella infected mother should receive oral acyclovir 15 mg/kg every 8 h within the onset of rash in order to treat the disease and to reduce the rate of complications. Women who are exposed to VZV should receive immunoglobulin with 72–96 h of exposure. If birth occurs 7 days prior or after the onset of rash, VZIG should be given.

Strategies to prevent congenital CMV infection, including the use of hyperimmune globulin and development of maternal vaccine, have yet to yield positive results.

Termination of pregnancy or ultrasound surveillance is what is practiced conventionally in case of congenital rubella syndrome because of very high risk of congenital anomalies with no treatment option available.

In utero treatment

Parvovirus B19 infection leading to fetal hydrops and fetal anemia is targeted with Intrauterine blood transfusion if the fetal hemoglobin is below the gestational age mean, as it reduces the risk of fetal death (OR 0.14; 95% CI 0.02–0.96).

Conclusion

The approach to the prenatal diagnosis of congenital infection varies according to the gestational age and the likely infectious agent. An essential common step is to confirm maternal infection, most frequently serologically,

by testing for pathogen-specific IgG and IgM. Avidity testing helps to differentiate old from recent infection. The risk of transmission to the fetus and the chance of fetal damage relate specifically to the pathogen and gestation at infection. Amniocentesis to test for the presence of RNA or DNA by PCR is the mainstay of diagnosis of fetal infection in most cases but the timing of the test in relation to the likely point at which transmission occurred is crucial. Furthermore, the detection of virus alone is not synonymous with fetal damage and a negative result does not completely exclude the possibility of fetal infection.

Ultrasound surveillance is the primary tool for determining the degree of damage but it, too, has limitations in accurately predicting the outcome for the baby. There are few therapeutic options for the infected fetus and these are currently limited to intrauterine blood transfusion in cases of anemia due to parvovirus infection.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.