Management of Viral Infection during Pregnancy

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Abstract: Viral infection during pregnancy should be handled from two main aspects, maternal management and the prevention of mother-to-child transmission. Infectious diseases in pregnant women are likely to become severe because cellular immunity is suppressed during pregnancy. Therefore, careful management is necessary in this population. The virus infecting the mother's body may be transmitted to the fetus or neonate through the following three routes: intrauterine transmission, intrapartum transmission, and transmission via breast milk. It is difficult to prevent intrauterine transmission, and therefore preventing maternal infection is prudent. Since the rubella vaccination rate has been decreasing recently, there is concern that the prevalence of antibody among pregnant women may decline as well. Maternal varicella infection in early pregnancy is said to result in congenital varicella syndrome in about 2% of infants born to infected mothers. About 10% of pregnant women who have been infected with human parvovirus B19 in early pregnancy reportedly experience miscarriage, and some of them are associated with fetal hydrops. Mother-to-child transmission of hepatitis B virus can be prevented in more than 90% of cases through the use of HBIG and HB vaccine. Mother-to-child transmission of viral infectious diseases is responsible not only for fetal or neonatal diseases but also for adult diseases. Therefore, collaborative studies involving the fields of obstetrics and gynecology, pediatrics, internal medicine, ophthalmology, and otolaryngology are required.

Key words: Mother-to-child transmission; TORCH syndrome; Preventive vaccination

Introduction

This paper discusses viral infection and maternal and child management in connection with the themes of pregnancy and interdisciplinary cooperation, and refers to new developments in the area of TORCH syndrome. TORCH is an acronym coined in the 1970s from the names of various infectious diseases that can lead to abnormal child birth if the mother is infected.
During pregnancy: T stands for toxoplasma, O for other (syphilis), R for rubella, C for cytomegalovirus, and H for herpes simplex virus. Subsequently, attention was given to a number of pathogens that affect the fetus through mother-to-child transmission, among them varicella virus, parvovirus B19, hepatitis B virus, adult T cell leukemia virus, Chlamydia trachomatis, and group B streptococci. Because of space limitations, this paper will focus on viruses and toxoplasma.

From the standpoint of interdisciplinary cooperation, two issues are of concern; the management of infected pregnant women and the possibility of pediatric, medical, ophthalmic, and otolaryngologic diseases of children infected through mother-to-child transmission.

**Consequences of Mother-to-child Transmission**

When the immunologically immature fetus or newborn is infected with a pathogen that has invaded the mother’s body, various consequences may result. These consequences include a wide spectrum of abnormalities and illnesses ranging from miscarriage, stillbirth, premature delivery, deformity, congenital infection, neonatal infection, and infantile infection to diseases that manifest in adulthood. For example, infants who become carriers of the hepatitis B virus through mother-to-child transmission may develop chronic hepatitis, resulting in cirrhosis and hepatic carcinoma 30–40 years later. Adult T cell leukemia virus can also produce carriers via mother-to-child transmission, and these infants develop leukemia when they become adults. Diseases in children and adults currently known to be caused by agents transmitted from mother to child as a possible route are shown in Table 1.

**Management of Infectious Diseases in Pregnant Women**

First of all, the disease of the pregnant woman herself should be treated, but the presence of the fetus should always be borne in mind during such treatment, with drugs that might otherwise be used routinely administered with caution. Next, management focused on the prevention of mother-to-child transmission is necessary. For this purpose, it is necessary to know the route and time of mother-to-child transmission. Mother-to-child transmission can occur in three ways: intrauterine transmission, intrapartum transmission (transmission in the birth canal), and transmission via breast milk. Although it is often difficult to prevent intrauterine transmission, intrapartum transmission can be prevented by cesarean section and transmission via breast milk by avoiding breast feeding.

Table 1 shows the classifications of routes of major infectious diseases involving mother-to-child transmission, although not all cases of mother-to-child transmission can be classified into these three categories in such a clear-cut manner. Rubella virus infection and toxoplasma infection, which are particular problems in cases of primary infection occurring during early pregnancy, are generally transmitted in utero. In contrast, herpes simplex virus infection and hepatitis B virus infection are generally transmitted during delivery. Intrapartum transmission may occur when the fetus comes in contact with maternal blood in the parturient canal or when the maternal blood is transferred to the
fetus as a result of labor pains. This route is important for the mother-to-child transmission of hepatitis B virus and HIV infections because the pathogens are present in the maternal blood.

Taking into consideration these mechanisms of transmission, the author has divided the practical prevention of mother-to-child transmission into four stages. In the stage of primary prevention, infection of the mother should be prevented. For instance, women who want to conceive should have established immunity to rubella in advance. In the second stage of prevention, mother-to-child transmission should be prevented by implementing treatment of the infected mother. Reduction of the amount of HIV in HIV-carrying mothers by antiviral drug therapy is an example. Tertiary prevention involves cesarean section to prevent transmission in the parturient canal and avoidance of breast feeding to prevent transmission via breast milk. The final stage of prevention involves the inhibition of clinical manifestations of disease in the infected child preemptive therapy. For instance, children born to mothers who carry hepatitis B virus will be given HBIG and HB vaccine, and children born to mothers who have had varicella during the perinatal period will be given high-titer varicella-zoster immune globulin (VZIG).

**Individual Diseases**

**1. Rubella virus**

It is well known that 30–50% of pregnant
women infected with rubella during early pregnancy deliver infants with congenital rubella syndrome (CRS). To prevent the birth of infants with CRS, it is most efficient to establish immunity in women before pregnancy. Since CRS is widespread in years when rubella is common among children, it is important to suppress epidemics of rubella. In 1994, the previous preventive vaccination law was revised, and, with the new revision, the earlier procedure of mass immunization with rubella vaccine in the second year of junior high school gave way to immunization on a voluntary basis in infants up to 90 months old and male and female junior high school students. With the implementation of this procedure, epidemics of rubella, which have tended to occur every 5–6 years, are considered to have been eliminated, together with a probable decrease in the incidence of CRS. However, the change from scheduled mass immunization to voluntary immunization has caused the vaccination rate among infants up to 90 months old and male and female junior high school students to fall to less than 50%. An increased proportion of seronegative individuals may be an issue when such individuals reach reproductive age. This problem may be enhanced by the fact that epidemics of rubella have been eliminated, providing less chance for these seronegative individuals to catch rubella spontaneously. Rubella vaccination has been promoted by the Japan Medical Association and the Ministry of Health, Labor and Welfare (JMA News, May 5 2000 issue). These efforts should be expanded nationwide.

2. Varicella-zoster virus

The prevalence of antibody to varicella-zoster virus (VZV) seems to be approximately 90% among individuals in their 20s and 30s, and it is not uncommon for pregnant women to develop varicella. Since varicella occurring during pregnancy may be severe and is often complicated by pneumonia, due caution is necessary. If signs of pneumonia appear, early implementation of intravenous drip infusion of aciclovir is recommended.

It has become apparent that abnormalities may occur in the fetus if the mother has varicella. A large-scale German and British study revealed that the incidence of such abnormalities is 0.4% until 12 weeks of gestation, 2.0% at 13–20 weeks of gestation, and 0% after 21 weeks of gestation. The incidence of fetal abnormality is reportedly 0% if the mother develops herpes zoster. Abnormalities occurring in the fetus include scarring of the skin, ophthalmic abnormalities, and hypoplasia of the extremities. If a pregnant woman comes in contact with a varicella patient, prevention of infection is attempted by administering VZIG. No infants with abnormalities have been born to mothers who received such treatment (Table 3).

If the mother is infected with varicella at the time of delivery, neonatal varicella may develop through mother-to-child transmission of the virus. If infection with VZV takes place during

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<table>
<thead>
<tr>
<th>Time of infection</th>
<th>Incidence of congenital varicella syndrome</th>
<th>Infantile zoster</th>
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<tbody>
<tr>
<td>Varicella</td>
<td></td>
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</tr>
<tr>
<td>0–12 weeks</td>
<td>0.4% (2/472)</td>
<td>0.8% (4/477) (13–24 weeks)</td>
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<tr>
<td>13–20 weeks</td>
<td>2.0% (7/351)</td>
<td>1.7% (6/345) (25–36 weeks)</td>
</tr>
<tr>
<td>21–36 weeks</td>
<td>0% (0/475)</td>
<td>0%</td>
</tr>
<tr>
<td>VZIG therapy after exposure</td>
<td>0% (0/97)</td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td>0% (0/366)</td>
<td></td>
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</tbody>
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the period from 4 days before to 2 days after delivery, varicella in neonates is likely to be particularly frequent and severe. In this case, VZIG should be administered to the neonate just after birth, and aciclovir therapy should be given as needed. From the obstetric viewpoint, the onset of labor pains may be inhibited to allow birth to take place 7 or more days after the onset of varicella, by which time IgG antibody production begins in the maternal body.

3. Erythema infectiousum (fifth disease)

It was determined that parvovirus B19 causes this disease, and it soon became apparent that intrauterine transmission of the virus might cause miscarriage and premature delivery. A finding of particular interest was that fetal hydrops may occur, frequently resulting in stillbirth. Intrauterine transmission is considered to occur in about 30% of mothers infected with this virus, and about 10% suffer miscarriage or premature delivery. No vaccine against this virus is currently available. Infection in pregnant women may be mediated by their own children who have become infected in day care centers. It is also common for pregnant women who work in day care centers or nurses who work in pediatric departments to be infected via young children in the workplace. The possibility of fetal deformity as a result of intrauterine transmission of parvovirus B19 is considered almost nil.

4. Hepatitis B virus (HBV)

It has been more than 15 years since preventive measures were first taken on a national basis in response to the finding that the incidence of mother-to-child transmission is high among infants born to HB virus carriers who are negative for HBe antigen, and this group of infants was also subjected to similar, but somewhat simplified preventive measures. This project resulted in a marked decrease in the number of infants carrying HB virus, from 3,300 per year to 420 per year. Although the long-term benefits of this procedure initially were questioned, it has become apparent that children who underwent these preventive measures are still seronegative after 10 years, confirming the benefits of the procedure.

5. Herpes simplex virus (HSV)

HSV infection is not uncommon in pregnant women. It often takes the form of genital herpes. Fetal anomaly caused by the intrauterine transmission of HSV is extremely rare. A greater problem is the development of neonatal herpes caused by transmission in the birth canal. More than 95% of cases of mother-to-child transmission are preventable by abdominal delivery by cesarean section if herpetic lesions are found in the external genitalia or cervical canal of the uterus. It has been advocated that medication with aciclovir is feasible for the treatment of genital herpes in pregnant women. This is grounded on the recent finding that deformity does not appear to occur at a significantly higher rate in infants born to mothers who have received this drug. However, if there are only slight signs and symptoms, as in recurrent cases, topical application of an ointment containing anti-herpes virus is sufficient treatment.

Vaccination

Vaccination is contraindicated during pregnancy. Live vaccine in particular is an absolute contraindication because of the possibility of transmission to the fetus. It should be kept in mind that contraception is necessary for two months after the inoculation of rubella vaccine. However, fortunately, no cases have been reported of CRS infants born to high-risk mothers who received vaccination in the early
pregnancy period or who conceived soon after vaccination. It seems that attenuated rubella virus used for vaccination is less teratogenic.

In theory, vaccine made from inactivated virus has no effect on the fetus and, therefore, can be used in pregnant women. However, it is a general rule that inactivated vaccine should not be given to pregnant women. It is a difficult problem as to whether or not pregnant women should be inoculated with inactivated influenza vaccine when influenza is widely prevalent. In regard to the teratogenicity of influenza virus, a relationship with abnormalities of the central nervous system was previously suggested. However, this relationship is currently denied. It was also reported that mortality from influenza pneumonia would be high in pregnant women. If this is true, active use of vaccination should be considered; however, it is currently thought to be unlikely, and hence there appears to be no need for vaccination.

Conclusion

The consequences of mother-to-child transmission involve not only fetuses and neonates but also extend to older children and adults. Prospective studies of children after mother-to-child transmission are needed, particularly as collaborative research by pediatricians, ophthalmologists, otolaryngologists, and internists. Obstetric management should be reconsidered in light of the results of such studies.

The search is underway in the obstetric field for efficient strategies against rubella virus, cytomegalovirus, herpes simplex virus, and toxoplasma, all of which are transmissible via transplacental route and lead to the birth of abnormal infants even when infected mothers do not show any clinical signs and symptoms.

The decreased prevalence of antibody among pregnant women has recently been reported for some viruses. Increases in the incidence of primary infection in pregnant women and resultant increases in the incidence of fetal and neonatal anomalies are of recent concern.

REFERENCES

