Ministry of Higher Education

and Scientific Research

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THE TORCH INFECTIONS

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2020-2021

Dedication

It is a great pleasure to dedicate this work with my thanks and respect to my supervisor Prof. Dr. Ali Alhussaini for his valuable instruction

To my family with loyalty

To my Father and mother for his big support with great respect

And to all those who support me throughout my life (my family, my friends and all my colleagues) .

THE TORCH INFECTIONS

abstract

Toxoplasmosis, other (syphilis, hepatitis, zoster), rubella, cytomegalovirus, and herpes simplex, or TORCH infections, are a group of maternal infections that have few maternal symptoms, lack effective therapy and can have major consequences for the fetus. Prenatal diagnosis of these infections is generally inconclusive, and routine screening is not currently recommended, except for rubella.

Toxoplasmosis

The prevalence of congenital toxoplasmosis has been estimated to be between 1 in 1000 and 1 in 10,000 live births. 1 In Massachusetts and New Hampshire, universal screening revealed a prevalence of 0.82 confirmed cases per 10,000 births. 2 Congenital infection affects approximately 15% of pregnant women in the first trimester, 25% in the second trimester, and 60% in the third trimester. 3 Congenital infection's seriousness however, increases with gestational age. Spiramycin has been reported to decrease the rate of fetal infection by 60%.(4)

Toxoplasmosis is caused by the protozoan parasite Toxoplasma gondii. Wild rodents and cats carry the organism, which can survive in soil for long periods in its oocyst form. According to adult serologic screening, the prevalence of toxoplasmosis in the United States is 20–50 percent. .(5)

In Europe and Africa, the prices are much higher. Since 80 percent of acutely infected patients are asymptomatic, most people with positive serologic tests are unaware that they have had the disease. And if signs do present, they are either nonspecific or appear as a viral disease, implying mononucleosis. .(6)

A single, enlarged cervical lymph node is the most common clinical presentation among women who exhibit symptoms.(7) Negative test results for mononucleosis (5) Toxoplasmosis or cytomegalovirus (CMV) infection should be suspected. The disease is spread by oocytes found in the feces of infected cats, or by consuming or handling raw or undercooked meat (hand-to-mouth contact). Cats that are kept indoors to avoid wild rats and are only fed cooked food do not pose a danger. Additional cover is provided by careful handling of the cat litter. The perinatal risk of toxoplasmosis occurs only when the infection happens just before or during pregnancy.(8, 9) The risk is highest in the early weeks of pregnancy, as it is for most perinatal infections. Fortunately, in the first trimester, the organism is less likely to cross the placenta than later in the pregnancy. Because of the well-developed placental blood flow, the rate of perinatal transmission increases with gestational age. About 50% of women infected at any time during pregnancy will give birth to infected children if they are not treated.(5)

Spontaneous abortion is normal with first-trimester transmission, but if the fetus is infected and survives, the effects may be catastrophic. Development restriction, chorioretinitis, microcephaly, convulsions, skin rash, hepatosplenomegaly, pneumonitis, jaundice, and fever are all symptoms of congenital toxoplasmosis. The loss of neural tissue causes

intracranial calcifications. Anemia and thrombocytopenia are possible, but the results in the spinal fluid may be nonspecific. The majority of these babies (85%) die; however, those who survive are severely affected, especially neurologically: 80% have seizures, 60% are spastic, 50% are visually impaired, and 28% have hydrocephalus or microcephaly. The diagnosis is usually not made in the mother until anomalies on ultrasound are discovered or an affected child is born. A mononucleosis-like syndrome may often raise suspicion, particularly if the circumstances suggest it (ingestion of raw meat or contact with cats). The Sabin–Feldman dye test or an indirect immunofluorescent antibody was used to make the diagnosis. .(10)

The former is more precise, but it's also less common. To develop a diagnosis, one must show a conversion from negative to positive or a .rising titer in both cases

The challenge in diagnosing an acute infection is distinguishing it from a residual titer that indicates a previous infection. Antibodies to T. gondii, known as immunoglobulin M (IgM), will last for years in healthy people. IgG positivity and IgM test that is helpful,(11) and, more recently, detecting subsets of IgG antibodies produced only during the early stages of infection has gotten a lot of attention. A test for differential agglutination (1)(2) and immunoblot and enzyme-linked immunosorbent assay (ELISA) tests for IgG subclasses(13) are available. The Food and Drug Administration (FDA) and the Centers for Disease Control (CDC) in the United States performed a comprehensive study of the six most widely used commercial IgM kits in 1996. The sensitivity was 93.3 percent to 100 percent. The precision was 77.5 percent to 99

percent.(14) The FDA released a physician advisory in 1997, warning them of the drawbacks of serologic research.(15) Any positive IgM test result should be checked at a toxoplasmosis reference laboratory, such as the Palto Alto Medical Foundation's Toxoplasmosis Serology Laboratory. When an acute infection is diagnosed during pregnancy, it's critical to assess if fetal infection has occurred, so other options, such as abortion or potentially toxic drug therapy, aren't justifiable. if the fetus is not infected. Chorionic villus sampling, amniocentesis,(16) and cordocentesis(17) Many of these methods have been used in conjunction with fetal blood analysis. These specimens were evaluated using a variety of methods, including IgM examination, tissue culture, and mouse inoculation. A polymerase chain reaction (PCR) method has recently proven to be both accurate and fast. .(18) Hydrocephaly, intracranial calcifications, or hydrops found on ultrasound can be indirect signs of congenital Toxoplasma infection. (19) If the diagnosis is suspected at the time of birth, a histologic examination of the placenta, which must be fixed in formalin as soon as possible, will confirm it. Lymph node biopsy is used to make the diagnosis in a small percentage of cases.(20) Medical findings or a diagnosis identified in the mother are used to suspect the diagnosis in the newborn. A positive particular IgM test or a persistent or rising IgG titer confirms that it is of neonatal origin rather than maternal origin. The mother usually does not need treatment because, if their immune systems are healthy, most adults recover on their own. Clinicians should be particularly cautious if toxoplasmosis and acquired immune deficiency syndrome (AIDS) coexist, since toxoplasmosis symptoms are likely to be much more serious. There are two treatment options if an acute Toxoplasma infection is diagnosed

during pregnancy and preferably confirmed in the fetus. Because of the serious repercussions for the fetus Pregnancy termination should be provided, particularly if infection occurs in the first trimester. Another alternative is to treat the mother in order to lessen the fetal effects. According to evidence from European trials, such an approach may minimize the severity of congenital infection. .(21) Sulfadiazine, 1 g orally four times a day, and pyrimethamine, 25 mg orally four times a day, are both given for 28 days in the US regimen. (22) To mitigate the hematologic effects of pyrimethamine, a folic acid antagonist, folinic acid, 6 mg intramuscularly (IM) or orally three days a week, is recommended. It's best to stop pyrimethamine in the first trimester and sulfadiazine as close to term as possible. In Europe, spiramycin has proven to be safe, but it is not available in the United States. Nonetheless, It is available from the US Food and Drug Administration's Division of Special Pathogens and Immunologic Drug Products (301–827–2127) for the care of pregnant women. It should be noted that such treatment does not guarantee that a newborn will be free of toxoplasmosis symptoms. Pregnancies after that are rarely affected. The same medications are used to treat the symptomatic newborn; however, many courses are often needed. Only if the particular IgM test is positive or if IgG is stable or rising should infants with no symptoms be treated. Isolation isn't needed. Preventing infection during pregnancy and identifying infection during pregnancy to provide early care are the most clear ways to avoid congenital toxoplasmosis. Not consuming raw or undercooked foods, carefully washing fruits and vegetables, and wearing gloves when gardening or handling cat litter are all important ways to prevent infection. It is the best that litter be changed frequently

to avoid drying with resultant aerosol spread. Cats that are kept as house pets and eat only pasteurized, thoroughly cooked food do not pose a health danger. Prevention is much more complex than early detection of infection during pregnancy. Only 10% of immunocompetent women with acute infection experience symptoms, and maternal symptoms have no link to fetal infection. . Consequently, the only way to accomplish this purpose is by systematic screening. This requires identifying women at risk (those who are seronegative before pregnancy) and periodic testing during pregnancy. Such programs have been effective in France and Austria but have not yet been evaluated in the United States. In the United States, routine screening for toxoplasmosis is not currently recommended during pregnancy; however, screening is recommended for women who are HIV positive.

Rubella

During a rubella outbreak in 1941, Australian ophthalmologist Gregg identified the prototype of the perinatal infections for the first time. .(23) In epidemics, large numbers of cases occur, but the intermittent occurrence is low. Eighty to ninety percent of the adult population is resistant, and the susceptible population can be further decreased by the use of rubella vaccine. Nonetheless, isolated instances do occur, posing a direct danger to the pregnant woman and her unborn child. Although the incidence of rubella reached an all-time low in 1988, the incidence has steadily increased since then, peaking in 1990 at its highest level since 1982. There seemed to be two distinct outbreaks: (1) in locations in which unvaccinated adults congregate, such as

workplaces, colleges, and prisons, and (2) among children in religious communities with low levels of vaccination.(24) There has also been a rise in the number of cases of congenital rubella syndrome recorded, though the total number of cases is still very small. When rubella strikes during the first trimester, the virus is extremely cytopathic, and spontaneous abortion is the most common outcome. If the early pregnancy survives, the chances of the fetus experiencing any consequence are high (up to 70 percent)(25). The full-blown clinical photo, known as "expanded rubella syndrome," is difficult to differentiate from congenital toxoplasmosis or CMV infection without laboratory testing. Development restriction, cataracts, pneumonitis, deafness, heart disease, jaundice, hepatosplenomegaly, and reduced platelets are all common symptoms. The mortality rate is extremely high (up to 33 percent) Rubella symptoms are milder in the second trimester, and there may be no symptoms at all in the third trimester, except for a positive IgM antibody test in the cord blood. Unfortunately, the viral genome in neural tissue continues to remain dormant. The rubella virus may be activated in the second decade of life, causing fulminant panencephalitis in children who were born with minimal to no symptoms. .(22)

The infant with congenital rubella will shed the virus for up to a year, posing an infection risk to healthcare workers. Viruses can also be found in the placenta. The most common rubella issue encountered by clinicians is the exposure of a pregnant woman to an infected infant. A pediatrician's confirmation of the diagnosis is extremely beneficial. Although the clinical diagnosis is normally not complicated, enteroviral

infections, mild measles, and human parvovirus B19 all have similar symptoms.

As a result, serologic confirmation is required, particularly given the pregnancy implications. If the pregnant woman has already been tested and found to be immune, only reassurance is needed. If her condition is unknown, a hemagglutination inhibition (HI) titer should be performed right away, and a part of the serum should be frozen. .(26)

Since later research would be less discriminating, this should be performed within 10 days of exposure. If this initial test reveals the presence of antibody, the patient should rest assured that she has been immune to a previous exposure or vaccine. For reassurance, some people retake the test after four weeks. If there is no detectable antibody in the initial test, the patient should be observed for development of clinical illness and repeat titers should be done at 2 - 4 weeks. Approximately one-third of adults who contract rubella show no symptoms. To avoid problems caused by differences in technique, all samples should be frozen and tested in the same laboratory at the same time. A fourfold increase in titer and conversion from negative suggest acute infection, and the patient should be counseled accordingly. The patient should be confident if no antibody forms and no clinical infection appears. If a delay in examining the patient after exposure occurs for some cause, the HI titer can already be positive and hence useless in confirming the diagnosis. The presence of rubella-specific IgM within 28 days of the onset of symptoms is considered diagnostic. In IgM studies, cross-reactions between rubella and human parvovirus infections have

been recorded. As a result, interpreting low or ambiguous rubella-specific IgM values with caution is advised .(27) Since rubella is not a severe disease, the mother's treatment is limited to symptomatic steps. Gamma globulin is not recommended because it may alter the clinical illness without preventing fetal effects. If the patient is reluctant to consider termination in any conditions, gamma globulin can be considered if both parties agree that there is no evidence that it would protect the fetus. Essentially, effective treatment for the rubella-infected gravida is to provide her with the knowledge she needs to make an informed decision about whether or not to continue the pregnancy. With the development of rubella vaccine, there is now at least the theoretical possibility for preventing congenital rubella. Because natural immunity protects 80–90% of women in the reproductive age group, the remainder might be covered by childhood immunization.

Unfortunately, this technique has not been effective, as a large portion of those who have been immunized lose detectable antibody after 5–10 years. While it is still recommended that all children are immunized (around 15 months of age), women must be retested and vaccinated if antibody is not identified before they enter childbearing age. This can only be achieved if the woman is not pregnant and will not be able to conceive for at least three cycles. Including the fact that the vaccine virus appears to pose much less fetal risks than the wild virus, (28) The vaccine virus does get into the products of pregnancy, and at least one case of alleged eye damage has been reported as a result of fetus infection with the vaccine virus. Since the introduction of the RA 27/3 rubella vaccine in 1979, a list of vaccine administrations during pregnancy has been held, and no evidence of congenital rubella

syndrome has been found among 272 susceptible, 32 resistant, and 379 women of uncertain immunity. Previous studies of women who received the Cendehill or HPV-77 vaccines during pregnancy found no signs of congenital rubella syndrome .(29) Based on this information, there is no cause to recommend pregnancy termination for women inadvertently vaccinated during pregnancy. An alternative time for the vaccination of susceptible women is immediately postpartum, when conception is less likely. Breastfeeding is not contraindicated for the vaccinated mother. Patients should be tested for immunity before vaccination, and because there is a 5 percent failure to develop antibody, follow-up titers should be done in 6–12 weeks. If no titer has formed, revaccination is recommended. Complications are uncommon, with transient arthralgia being the most common. The quest for more powerful vaccines that can provide more comprehensive defense continues.

Cytomegalovirus

The most common TORCH infection that affects newborns is cytomegalovirus. It's the most common cause of hearing loss and neurological disability in children. (30) It's a double-stranded DNA virus that belongs to the herpesvirus family. It, like other members of this family, can go into dormancy and then reactivate at a later date. CMV is contracted by 1–2% of all newborns, and about 10% of these babies will show signs of harm if they are closely monitored. This means that a major neonatal infection occurs once every 500 to 1000 births. Congenital transmission of CMV can occur during pregnancy as a result of primary infection, reactivation, or recurrent maternal infection, though the risk of congenital infection is much higher with primary

infection (30–40% versus less than 1% with recurrent infection). Recurrent CMV infection in the mother is more common than primary infection (1–14% vs. 0.7–4%). 31 CMV is acquired steadily from birth to reproductive age, at which point 50% of women have serologic evidence of previous infection.(12) CMV is spread by sexual contact or contact with contaminated blood, saliva, or urine. CMV is found in the endocervical fluid of 3–5% of sexually active women. This allows for more exposure during the birthing process. Transmission in healthy adults necessitates prolonged or frequent physical touch. The time of incubation is 30–60 days. In adults with healthy host defenses, CMV is normally asymptomatic. Malaise, fever, headache, and myalgia are some of the most common symptoms. Relative lymphocytosis and thrombocytopenia can be found in the laboratory. A moderate increase in liver enzymes is also possible. The majority of infections go away in 2–6 weeks. CMV is common and dangerous in immunocompromised patients that have had organ transplants or are undergoing cancer chemotherapy. Pregnant healthcare workers are at risk from these patients. CMV can also be transmitted by blood transfusions, resulting in an enigmatic fever in patients that have recently been transfused. (25) Most often, however, the diagnosis is unsuspected until the birth of an affected infant. Confirmation of the diagnosis is not simple.(32) The large number of patients with antibodies from previous exposure complicates serologic research. Also advanced techniques like ELISA and the neutralizing antibody test don't always reveal the reality. Rapidly rising titers and a particular IgM are good indicators, but they can take a long time to appear. . The most effective diagnostic method is virus isolation, but the process can take up to 6 weeks. The fetus may be infected at any

point of pregnancy, as with the other TORCH diseases, but the symptoms are most serious when it happens early. (33) More severe sequelae are seen in children of mothers with primary infection. Ten to fifteen per cent of infants with congenital CMV infection are symptomatic at birth. Maternal infection in the first trimester can result in a full-blown syndrome similar to that seen with toxoplasmosis and rubella. Manifestations include growth restriction, microcephaly, intracranial calcifications, chorioretinitis, hepatosplenomegaly, and disseminated intravascular coagulation. The mortality rate among symptomatic infants is 20–30%. Ninety per cent of those who survive have serious neurological sequelae.(34) Clinical manifestations include mental retardation, seizures, hearing loss, visual problems, and developmental delay. Asymptomatic infants are also at risk, for 5–15% of them are found to have neurological sequelae, especially sensorineural hearing loss.(35) Differentiation from other TORCH infections generally requires laboratory assistance. With infection later in pregnancy, the fetal effects are less serious, and in the third trimester the only apparent result may be a positive specific IgM or viral isolation. The question of long-term effects is not completely settled.(36) Some have reported a definite association with deafness, but the relationship to learning disabilities, for example, is less clear. There are isolated reports of fetal infection as the result of intrauterine transfusion. Neonatal infection can occur from multiple sources, including breast milk, and is characterized by pneumonia and hepatosplenomegaly.

Currently, there is no effective therapy for CMV infection during pregnancy. Ganciclovir is used to treat CMV in immunocompromised patients. It has hematologic toxicity. Treatment with ganciclovir during

pregnancy has not been shown to prevent congenital CMV infection.(37) The diagnosis is rarely established during pregnancy, but this presents the only opportunity for intervention. The pregnant woman who presents with a mononucleosis-like syndrome should be carefully evaluated for CMV infection. If the diagnosis is confirmed, she can be offered counseling with regard to the prognosis and the possibility of termination.38 As with other perinatal infections, there are increasing numbers of reports of confirmation of the diagnosis of CMV in the fetus. Viral isolation from amniotic fluid, cordocentesis with serologic testing, and viral culture have been reported.(39), (40) Reports suggest that PCR done on amniotic fluid samples obtained after 21 weeks' gestational age appears to be a reliable method of detecting CMV infection, even after a 7-week interval.(41) There may be a relationship between the quantity of CMV detected in the amniotic fluid and the presence of fetal abnormalities. Higher quantities of viral DNA were identified in the amniotic fluid of symptomatic fetuses and newborns compared to those without symptoms.42 Prenatal detection of intracranial calcifications has also been reported, but this usually occurs too late in gestation to provide useful options.(43)

Recent studies by Nigro and colleagues have shown a significant reduction in both the incidence and severity of congenital CMV with the use of passive immunization with hyperimmune globulin (CMV HIG).(44), (45) Likewise, there is no specific therapy for the affected newborn though neonatal treatment with ganciclovir showed prevention of hearing loss progression.(46) Isolation is indicated, however, because both the infant and the placenta are infectious. Subsequent pregnancies are rarely affected.

There is considerable effort underway to develop a CMV vaccine.(47) this is primarily directed toward patients who will undergo organ transplantation. The work has been hampered by the fact that the virus does not always express its genome completely in tissue culture. There is also the concern that the vaccine strain may reactivate and shed from the cervix and into the breast milk. There is even a concern about oncogenicity. For these reasons, the application of the vaccine in preventing perinatal infection is not imminent. Women of childbearing age should be educated about CMV infection and transmission. They should be cautioned about the careful handling of soiled diapers. Effective hand washing is critical in the presence of young children and immunocompromised individuals..

Acknowledgments

I sincerely express my gratitude to my supervisor Prof. Dr. Ali Alhussaini for suggesting this article review , his great support, guidance, patience, continuous generous help and fruitful scientific instructions throughout the course of article.

Deep gratitude and special thanks go to all the teaching staff of Diyala College of Medicine for their scientific lectures and practical assistance.

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