REVIEW ARTICLE

Maternal Infections Associated with Bad Obstetric Outcome: Toxoplasmosis and Rubella.

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Toxoplasmosis:

1. Overview.

Toxoplasmosis is caused by infection with the obligated intracellular protozoan parasite *Toxoplasma gondii*. It is one of the most prevalent chronic infections affecting one third of the world's human population [1]. The prevalence of *T. gondii* infection varies among different geographical regions. The infection is characterized by non-specific signs with the consequent formation of cysts that may stay in latent form in many organs [2]. Primary infection is usually subclinical but in some patient's cervical lymphoadenopathy or ocular disease can be present [3].

There are four groups of individuals in whom the diagnosis of toxoplasmosis is most critical: pregnant women who obtain their infection during gestation, fetuses and newborns who are congenitally infected, immune compromised patients, and those with chorioretinitis [4]. Although these infections are usually either asymptomatic or associated with self-limited signs in adults [e.g., fever, malaise, and lymphoadenopathy], infections in pregnant women can cause severe health problems in the fetus if the parasites are transmitted [i.e., congenital toxoplasmosis] and cause severe sequelae in the infant including mental retardation, blindness, and epilepsy [5].

The most repeated experiment encountered by physicians over the World is how to determine if a pregnant woman acquired the acute infection during gestation. Women who acquired their infection prior to pregnancy are essentially not at risk for delivering an infected infant [unless the woman is immunosuppressed]. Practicing obstetricians may be confronted with a number of issues regarding toxoplasmosis, including diagnosis, laboratory testing, screening practices, clinical presentation, and prevention [6].

Although congenital toxoplasmosis is not a nationally reportable disease, extrapolation from regional studies indicates that an estimated 400 to 4,000 cases occur in the U.S. each year [7]. The overall laboratory evidence of an infection of *T. gondii*, at a prevalence rate of 23%, emphasizes the scope of toxoplasmosis in a community, and it explains the heavy burden of morbidity due to this parasitic disease [1]. It is supposed that congenital toxoplasmosis results from a primary infection acquired during pregnancy, but not from the reactivation of a latent infection in immunocompetent pregnant women . In addition, it is believed that latent toxoplasmosis could reactivate and cause a congenital transmission of the parasite to infants who then develop infected in utero [8].

In recent years, a major effort has been made toward improving our ability to diagnose recently acquired infection in the pregnant woman and congenital infection in the fetus and newborn. We now have an amount of new methods that are proving to be of great value towards an end. Among these are the serum IgG avidity test, PCR with body fluids and tissues, and Western blots of serum from mother-baby pairs [9].

Infections with *T. gondii* during early pregnancy may frequently lead to many intrauterine malformations. The detection of anti-toxoplasma antibodies by ELISA [Enzyme-Linked Immunosorbent Assay] methods is commonly done in many medical centers. The results of such tests are generally well accepted by clinicians because of their excellent sensitivities and specificities, the rapid availability of results, and the relatively low costs of the tests. It is important to understand that a single serologic test is not enough for the diagnosis of toxoplasmosis [10]. In worldwide, commercial test kits for Toxoplasma-specific IgG and IgM antibodies are readily available. Since IgM antibodies can be detected for many months or even years following the acute phase of an infection in some individuals, the presence of IgM antibodies is not always an indication of a recent infection [11]. On the other hand, the presence of specific *T. gondii* IgM antibodies in the chronic phase of an infection, and false-positive IgM positivity results can lead to and result in needless concern and a misdiagnosis [possibly affecting the decision to abort] particularly in pregnant women [12].

IgM test results are difficult to interpret and the reliability of test kits is variable. Some commercial IgM tests have had problems with specificity, resulting in unacceptably high rates of false-positive test results. In 1996, the Food and Drug Administration [FDA] and Centers for Disease Control [CDC] conducted extensive evaluations of the six most commonly used commercial IgM kits in the U.S. to determine the range of the problem with the specificity of these kits. Sensitivity and specificity rates for these six kits ranged from 93.3% to 100.0% and from 77.5% to 99.1%, respectively [13].

Although the sensitivity and specificity seem acceptable, this study design could not determine the extent of false-positive results. The Food and Drug Administration [FDA] has noted problems with false-positive results in some testing methods, and the CDC has responded by creating a toxoplasma serum panel with known positive and negative sera. The FDA now requires new commercial test kits to use this sera as the "gold standard" during quality assurance testing ,False positives are a major concern because they create anxiety-ridden pregnancies, expose fetuses to unnecessary procedural dangers of diagnosis and side effects of treatment, and may ultimately lead to termination of a non-infected pregnancy [14].

2. Specific Laboratory Tests

2.1. IgM and IgG Detection.

Initial maternal serological screening trusts on identification of IgG and IgM antibodies using ELISA, the presence of elevated levels of Toxoplasma specific IgG antibodies indicates infection has occurred at some point, but does not distinguish between an infection acquired recently and one acquired in the distant past. In acute infection IgG and IgM antibodies generally rise within 1 to 2 weeks of infection acute toxoplasmosis is diagnosed rarely by detecting the parasite in body fluids, tissue, or secretions the greatest common method used worldwide in the attempt to determine if and when a pregnant woman has experienced acute infection with toxoplasmosis [4]. Detection of Toxoplasma-specific IgM antibodies

has been used as an aid in determining the time of infection, but IgM antibodies have been reported to continue for up to 18 months post infection [13]. A negative IgM with a positive IgG result indicates infection at least 1 year previously. A positive IgM result may indicate further recent infection or may be a false positive reaction.

There are different Toxoplasma seropositivity reports from all over the world. The population of Turkish childbearing age women has the seropositivity of *T. gondii* as 1.34% for IgM and 24.6% for IgG, In Maracaibo, Venezuela the overall prevalence of toxoplasmosis was 33%, while 18.2% were positive IgM [15]. In Qatar among 823 women of childbearing age the *T. gondii* IgG and IgM was 35.1% and 5.2%, respectively [16]. In a study in Beirut the seroprevalence of IgG *T. gondii* antibodies from 2145 sera were examined in hospital and private laboratories and the seropositivity rates were found to be 55% and 67%, respectively.

2.2. IgG Avidity Test.

Since the U.S. Food and Drug Administration [FDA] has recommended that a solely positive IgM test result should undergo confirmatory testing, avidity specific *T. gondii* IgG tests have been presented to differentiate between recently acquired and distant infections [7]. Recently, it has been discovered that IgG avidity tests can provide confirmatory evidence of an acute infection and they can distinguish reactivations from primary infections with a single serum specimen [17].

2.3. IgA Antibodies.

Toxoplasma specific IgA has been measured both by enzyme linked immunosorbent assay [ELISA] and immunosorbent agglutination assay [ISAGA], in the sera of patients with acquired primary infection. After infection it is claimed that specific IgA production parallels that of specific IgM or lgA slightly behind IgM, The increased sensitivity of IgA assays over IgM assays for diagnosis of congenital toxoplasmosis [18].

2.4. IgE Antibodies

Beside its critical role in allergy, IgE is generally believed to play a physiological role in immunity towards helminthic parasites. Immune response to parasite infection is often correlated with an increased expression of IgE in mammals, which is believed to play a protective role against worms IgE antibodies are detectable by ELISA in sera of acutely infected adults, congenitally infected infants, and children with congenital toxoplasmic chorioretinitis [19].

2.5. Histological Diagnosis

Demonstration of tachyzoites in tissue sections or smears of body fluid [e.g., CSF, amniotic fluid or BAL] determines the diagnosis of the acute infection. It is often difficult to demonstrate tachyzoites in conventionally stained tissue sections. The immunoperoxidase technique, which uses anti sera to *T. gondii* , has proven both sensitive and specific; It has been successfully used to demonstrate the presence of the parasite in the central nervous system of AIDS patients [20].

2.6. Polymerase Chain Reaction [PCR]

Confirmed positive maternal serological screening should be accompanied by fetal diagnosis. Prenatal diagnosis of congenital toxoplasmosis is primarily based on ultrasonography and PCR with amniotic fluid. The polymerase chain reaction [PCR] amplification of toxoplasmosis DNA from amniotic fluid has been deemed the most reliable and safe method of prenatal diagnosis and has basically replaced direct sampling of fetal blood ,Amniotic fluid testing by PCR is indicated in all

pregnant women with serologic test results diagnostic of acute infection acquired during gestation [21].

Rubella virus

1. Introduction:

Rubella is a mild disease caused by a togavirus. There may be a mild prodromal illness involving a low-grade fever, malaise, coryza and mild conjunctivitis. Lymphadenopathy involving post-auricular and sub-occipital glands may lead to rash. The rash is usually transitory, erythematous and mostly seen behind the ears and on the face and neck. Clinical diagnosis is unreliable as the rash may be fleeting and is not specific to rubella. Rubella is spread by droplet transmission. The incubation period is 14 to 21 days, with the majority of individuals developing a rash 14 to 17 days after exposure. Individuals with rubella are infectious from one week before symptoms appear to four days after the onset of the rash. Complications include thrombocytopaenia (the rate may be as high as one in 3000 infections) and post-infectious encephalitis (one in 6000 cases) [22].

Epidemiology:

Before the introduction of rubella immunization, rubella occurred commonly in children, and more than 80% of adults had evidence of previous rubella infection .Rubella immunisation was introduced to the UK in 1970 for pre-pubertal girls and non-immune women of childbearing age to prevent rubella infection in pregnancy. Rather than interrupting the circulation of rubella, the aim of this strategy was to directly protect women of childbearing age by increasing the proportion with antibody to rubella; this increased from 85 to 90% before 1970 to 97 to 98% by 1987 [23].

Surveillance for congenital rubella began in 1971 to monitor the impact of the vaccination programme. During the period 1971–75 there were an average of 48 CRS births and 742 terminations annually in the UK .Although the selective immunisation program was effective in reducing the number of cases of CRS and terminations of pregnancy, cases of rubella in pregnancy continued to occur. This was mainly because the few women who remained susceptible to rubella could still acquire rubella infection from their own and/or their friends' children [24].

A seroprevalence study in 1989 showed a high ratio of rubella susceptibility in school-age children, particularly in males. In 1993, there was a large increase in both notifications and laboratory-confirmed cases of rubella. Many of the individuals affected would have not been eligible for MMR or for the rubella vaccine. For this reason, the combined measles-rubella (MR) vaccine was used for the schools campaign in November 1994. At that time, insufficient stocks of MMR were available to vaccinate all of these children against mumps. Over 8 million children aged between 5 and 16 years were immunised with the MR vaccine [25].

In October 1996, a two-dose MMR schedule was introduced and the selective vaccination policy of teenage girls ceased. A single dose of rubella-containing vaccine as used in the UK confers around 95 to 100% protection against rubella .In Finland, a two-dose MMR schedule was introduced in 1982; high coverage of each dose has been achieved consistently. Indigenous measles, mumps and rubella have been eliminated since 1994.The United States introduced its two-dose schedule in 1989 and, in 2000, announced that it had interrupted endemic transmission . MMR is now routinely given in over 100 countries, including those in the European Union, North America and Australasia [26].

2. Congenital Rubella Syndrome.

Congenital rubella is a condition that occurs in an infant whose mother is infected with the virus that causes German measles. Congenital rubella occurs when the rubella virus in the mother affects the developing baby at a critical time, in the first 3 months of pregnancy. After the fourth month, the mother's rubella infection is less likely to harm the developing baby. The number of babies born with congenital rubella has decreased dramatically since the introduction of the rubella vaccine. Pregnant women who are not vaccinated for rubella and who have not had the disease in the past risk infecting themselves and their unborn baby. Signs in the infant may include: Cloudy corneas or white appearance to pupil, Deafness, Developmental delay, Excessive sleepiness, Irritability ,Low birth weight, Intellectual disability, Seizures, Small head size, Skin rash at birth [27].

Vertical Transmission and Risk of CRS.

Fetal infection is acquired hematogenously, and the rate of transmission varies with the gestational age at which maternal infection occurs. After infecting the placenta, the rubella virus spreads through the vascular system of the developing fetus, causing cytopathic damage to blood vessels and ischemia in developing organs. When maternal infection exposure occurs in the first trimester, fetal infection rates are near 80%, dropping to 25%in the late second trimester and increasing again in the third trimester from 35% at 27–30 weeks' gestation to nearly100% beyond 36 weeks' gestation [28].

The risk of congenital defects has been reported to be 90% when maternal infection occurs before 11 weeks of gestation, 33% at 11–12 weeks, 11% at 13–14 weeks, 24% at 15–16 weeks, and 0% after 16 weeks. Therefore the risk of congenital defects after maternal infection is essentially limited to the first 16 weeks of gestation. Little, if any, risk of CRS is associated with infection beyond 20 weeks, and FGR seems to be the only sequelae of third trimester infection. Periconceptual maternal infection does not seem to increase the risk of CRS.18 Maternal immunity, either after vaccination or naturally derived, is commonly protective against intrauterine rubella [29].

3. Laboratory Testing

3.1. Virus detection (real-time RT-PCR).

Rubella virus can be detected from nasal, throat, urine, blood, and cerebrospinal fluid specimens from persons with rubella .Virus may be detected from 1 week before to 2 weeks after rash onset. However, maximum viral shedding occurs up to day 4 after rash onset, Real-time RT-PCR and RT-PCR can be used to detect rubella virus and has been widely evaluated for its usefulness in detecting rubella virus in clinical specimens [30].

3.2. Serologic testing

3.2.1. Detection of IgM antibody.

Rubella-specific IgM can usually be discovered 4–30 days after onset of illness, and often for longer. Sera should be collected as early as possible after onset of illness. However, IgM antibodies may not be noticeable before day 5 after rash onset. In case of a rubella IgM-negative result in specimens taken before day 5, serologic testing should be repeated on a specimen collected after day 5.Because rubella incidence is low, a high proportion of IgM-positive tests will likely be false positive. False-positive serum rubella IgM tests may occur due to the presence of rheumatoid

factors (indicating rheumatologic disease) or cross-reacting IgM, or infection with other viruses. Avidity testing (see below) and detection of wild-type rubella virus can be used to resolve uncertainties in the serologic evaluation of suspected cases [31].

3.2.2. Detection of IgG antibody (significant rise or avidity) for diagnostic testing

To notice a significant rise in rubella-specific IgG concentration, the first serum should be obtained as soon as possible after onset of illness and the second serum sample should be collected about 7–21 days after the first specimen. In most rubella cases, rubella IgG is detectable by 8 days after rash onset, tests for IgG antibody should be conducted on both acute-and convalescent-phase specimens at the same time with the same test [32].

3.2.3. Detection of IgG antibody to screen for rubella immunity:-

A single serologic IgG test may be used to determine the rubella immune status of persons whose history of rubella disease or vaccination is unknown. The presence of serum IgG rubella-specific antibodies indicates immunity to rubella [33].

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