J. Fetal Med. (March 2020) 7:25–29
https://doi.org/10.1007/s40556-019-00232-8

REVIEW ARTICLE

# Epidemiology of TORCH Infections and Understanding the Serology in Their Diagnosis

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Received: 7 August 2019 / Accepted: 12 November 2019 / Published online: 2 January 2020


**Abstract** TORCH, as coined by Nahmias et al. consists of Toxoplasmosis, other infections (includes, syphilis, HIV, Hepatitis viruses, varicella virus and Parvovirus B19), Rubella, Cytomegalovirus (CMV) and Herpes simplex virus. These infections are transmitted prenatally, perinatally, and postnatally through transplacental passage, contact with blood and vaginal secretions or from exposure to breast milk for CMV, HIV and HSV and infection generally manifests at birth, in infancy or in later years of life. The disease burden is maximum in low to middle-income countries. As treatment and prevention strategies are available for most of these infections, early recognition including prenatal serological screening are important. But routine full screening of 'TORCH panel" is not recommended in low risk asymptomatic pregnant women. It is indicated in pregnancies with congenital infections, fetal hydrops, fetal brain lesions, unexplained IUGR, in pregnant women with non-vesicular rash or other signs and symptoms suggestive of systemic infections or in women with a history of contact with a person with such illness. The following article highlights the importance of serological tests for the diagnosis of TORCH infections.

**Keywords** Toxoplasma · Rubella · Cytomegalovirus · Human herpes virus · Treponema · Syphilis

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## Introduction

The acronym **'TORCH'** was first coined in 1971 by Nahmias et al. [1] to stand for Toxoplasmosis, other infections (includes, syphilis, HIV, Hepatitis viruses, varicella virus and Parvovirus B19), Rubella, Cytomegalovirus (CMV) and Herpes simplex virus (HSV). However, most clinical laboratories continue to offer 'TORCH serology' typically for Toxoplasmosis, Rubella, CMV and HSV 1 and 2. These infections are generally transmitted prenatally, perinatally, and postnatally through the transplacental passage, contact with blood and vaginal secretions or from exposure to breast milk for CMV, HIV and HSV. The infections with these organisms may become apparent at birth, in infancy or in later years of life even after many years [2]. The epidemiology of these infections varies, with the maximum disease burden being in the low to middle income-countries [3].

Since most of these maternal infections are initially asymptomatic and the clinical diagnosis is also unreliable due to overlapping signs and symptoms, diagnosis of these infections is generally based on serological evidences [4]. As treatment and prevention strategies are available for most of these infections, early recognition including prenatal screening are important. Routine full screening of 'TORCH panel" is not recommended in low risk asymptomatic pregnant women. Screening of TORCH panel is indicated in pregnancies with congenital infections, fetal hydrops, fetal brain lesions, unexplained IUGR, in pregnant women with non-vesicular rash or other signs and symptoms suggestive of systemic infections or in women with a history of contact with a person with such illness [5].

In this review, we have focused on the importance and interpretation of serological tests for the diagnosis of TORCH infections. We also briefly review the role of serological tests in the diagnosis of Toxoplasmosis,

**Table 1** Interpretation of the immune response to toxoplasma infection

| IgG | IgM | Interpretation | Further action |
|---|---|---|---|
| Negative | Negative | No past/recent infection | Educate and teach the hygienic practices to patient to prevent the infection in future |
| Positive | Negative | Past infection (> 6 months) | Immunity to toxoplasmosis. Subsequent pregnancies are safe |
| Negative | Positive | Very early positive infection or false positive | Repeat test in 2–4 weeks to see IgG seroconversion. False positivity is very common in IgM. If the repeat IgG still remains negative, it is most likely a false positive test and must be ignored |
| Positive | Positive | Suggestive of acute infection | Repeat test in 2–4 weeks. If rising titres/OD values/OD ratio, it is most likely an acute active infection. If stable or reducing, it is most likely false positive |
| | | | Do IgG avidity test |
| | | | If low → recent infection and requires treatment |
| | | | If high → infection of ≥ 4 months duration |

Syphilis, Parvovirus B19, Rubella, Cytomegalovirus (CMV) and Herpes simplex virus infections.

### *Toxoplasma gondii*

*Toxoplasma gondii* is an obligate intracellular parasite, being ubiquitous in the environment, with members of the feline family being the only definitive hosts. The infection is acquired by ingestion of undercooked meat containing cysts of *T. gondii* or due to ingestion of water or food contaminated with oocysts excreted in the cat faeces. After ingestion, toxoplasma acquires it's active form invades into the intestinal epithelial cells and then reaches the circulation [6].

Congenital infection in foetus generally results when mother acquires primary infection during pregnancy [7]. Immunocompromised mothers such as those infected with HIV or on chemotherapy, may rarely transfer the infection to foetus by the reactivation of latent primary maternal infection during pregnancy [8] and very rarely even without any predisposition [9] or if the infection occurs with different genotype of *T. gondii* [10]. The rate of vertical transmission in foetus increases with the increasing duration of pregnancy [11]. The risk of transmission in the first, second and third trimester is 15%, 30% and 60% respectively. However, the severity of illness is greatest in the early pregnancy [11].

The seroprevalence of toxoplasmosis varies amongst countries; with higher prevalence seen in countries with tropical climate as the oocysts can survive better in the environment in these areas. It is also seen to be higher in countries having practice of eating raw or half cooked meat [3, 6, 12]. The details are given in various recent reviews on the subject [3, 6].

The prevalence rate of toxoplasmosis in India during pregnancy is reported to be between 20 and 44% [6, 13]. The seroprevalence of toxoplasma IgG antibodies in various regions of India with regard to general population has been reported to range from 40 to 75% [12]. The prevalence of Toxoplasma IgG in women of child bearing age of Delhi and surrounding areas was reported to be between 25 and 28% [13, 14].

### Diagnosis

Usually, the first step in the diagnosis of toxoplasmosis is detection of serum anti-T.gondii IgG and IgM antibodies as a measure of the response to infection [3, 5, 12, 13, 15]. The commonly used tests are Enzyme linked Immunosorbent assay (ELISA) and IgG avidity test. Confirmatory tests like Sabin–Feldman dye test (gold standard), indirect immune -florescent antibody test are done only in reference laboratories. A diagnostic algorithm has been published earlier by the author [15]. A brief summary of the interpretation of IgG and IgM results is given below in Table 1.

### *Rubella Virus* (German or 3 Day Measles)

Rubella virus is an enveloped, single-stranded, positive sense RNA virus belonging to the family Togaviridae which is transmitted by the respiratory route with humans as the only natural reservoir. Transmission to the foetus generally occurs, if mother acquires rubella infection from 1 month before conception to second trimester of pregnancy. The frequency of transmission of congenital infection after maternal rubella is 70–85% in first trimester, 30–54% from 13 to 16 weeks of gestation and 10–25% at the end of second trimester. The classical triad of rubella also known as the Congenital Rubella Syndrome comprises of sensorineural deafness, microphthalmia, cataract and congenital heart diseases esp patent ductus arteriosus [16].

United States in 2004 had declared the elimination of rubella transmission and Congenital Rubella Syndrome (CRS). However, worldwide it is estimated that nearly 110,000 infants are born with CRS every year. WHO has targeted regional elimination of CRS by 2015 and rubella

elimination in five WHO regions by 2020 [16]. It is important to note that vaccinated or naturally infected, the individual remains immune for entire life. There are only a few studies published from India [17]. A study carried out in Delhi [17] and a review of literature [18] revealed that 10–30% of adolescent girls and 12–30% of women in the reproductive age-group are susceptible to rubella infection. The authors reported that CRS accounted for nearly 10% of paediatric cataract in India.

### Diagnosis

Diagnosis of rubella virus infection is generally done using the serological tests. IgM antibodies usually develop within 4–5 days after the onset of the infection and may remain positive up to 6 months and rarely for a much longer duration [12, 19]. The serological diagnostic algorithm is by and large similar to Toxoplasmosis, except that false anti-Rubella IgM positivity can also be seen in recently vaccinated cases. Therefore history of vaccination is most crucial to interpret the test results. IgG avidity test plays very important role in pinpointing the time of infection [12]. For amniotic fluid, CSF and other body fluids, PCR methods are available, but only few laboratories do these molecular tests due to easy availability and high sensitivity of serological methods.

## Cytomegalovirus

CMV belongs to the β herpesviruses of the Herpesviridae family. It is ubiquitous in nature and is the most common form of foetal infection occurring in 0.5–2% of all live births [20]. Pregnant women most commonly acquire infection by exposure to infected children at home or as an occupational hazard. Infection occurs by exposure to different body fluids such as saliva, semen, blood, urine and cervical secretions [21].

Maternal infection is generally asymptomatic with the mother generally being unaware of the infection. A small percentage of women may present with mononucleosis like symptoms such as malaise, myalgia, fever, lymphadenopathy etc. However, immunocompromised patients may develop severe complications such as pneumonia and chorioretinitis [20]. Maternal transfer of CMV occurs only in 0.5–2% women with pre-conceptional immunity. Congenital CMV infection can still occur in previously immune mothers due to reinfection with a new strain of the virus [22–24]. CMV causes congenital infection with mental retardation, microcephaly, chorioretinitis and many vague manifestations [12].

As mentioned in the above paragraph, in India, various studies have reported IgG seroprevalence amongst women of child bearing age to be 80–90% [20–26]. A study conducted at AIIMS, New Delhi in 2004 [12], showed the prevalence of CMV IgM antibodies to be nearly 20.2% in children with varied clinical manifestations of CMV e.g. hepatitis/cholestasis etc.

### Diagnosis

Due to very high seroprevalence of CMV in general population, diagnosis and especially the interpretation of test results is very complex and not straight forward as in the case of Rubella. The commonest method for the diagnosis of maternal infection is CMV IgM positive or very high IgG antibody titers [5]. The presence of IgM antibodies in the foetal or cord blood is a very sensitive and specific test for the detection of congenital CMV infection. The CMV avidity test is also available to determine if the infection is recently acquired. A low avidity indicates recent infection and high avidity indicates past infection. Highly sensitive and most specific PCR methods are available, but only few laboratories do these molecular tests due to easy availability and high sensitivity of serological methods.

## Herpes Simplex Viruses

Herpes Simplex viruses (HSV) belong to α Herpesviridae and consists of two viruses, HSV-1 and 2, which resemble each other at the molecular level and also in their clinical manifestations. [16, 20]. It has been classically described that HSV-1 causes lesions above the belt while HSV-2 causes lesions below the belt. However, recent studies [20, 27–29] show changing pattern of clinical manifestations especially in HIV infected individuals. The risk of transmission from pregnant women to an infant in individuals with primary genital herpes is 33–50% whereas in recurrent maternal infection is only 1–3% [30]. As per the WHO 2012 report [31], nearly 417 million people worldwide were seropositive for HSV-2. A recent study published in India shows that HSV-1 and HSV-2 infections are prevalent in 40% and 25.9% of adult males [32].

### Diagnosis

Nearly 90% of the women with genital herpes due to HSV-1 or HSV-2 are underdiagnosed as they are asymptomatic or their symptoms are incorrectly attributed to other vulvovaginal disorders [33]. Thus, a negative maternal history of HSV does not dissuade the clinicians from considering the possibility of neonatal herpes in infants with compatible signs and symptoms. All individuals with HSV-2 seropositivity are at high risk of transmitting infection during sexual activity, labour, delivery and intimate contact [16]. Thus, all women should be screened serologically for

HSV-1 and 2 antibodies and women with genital lesions at the time of delivery must be counselled for caesarean delivery, antiviral suppressive therapy and minimal invasive intrapartum procedures. Single-plex and multiplex PCR methods are available which can detect and differentiate HSV-1 and HSV-2 but only few laboratories do these molecular tests.

### Parvovirus B19

Parvovirus B19 causes erythema infectiosum or fifth disease [34]. If acquired during early pregnancy, this can lead to hydrops fetalis and fetal aplastic crisis. The maternal infection rate is highest in mothers having other school age children at home and in day care workers.

Globally, the seroprevalence of IgG antibodies in children of 1 to 5 years age is 2–15%; children of 6–19 years it is 15–60%; in adults it is 30–60% and in geriatric age group it is > 85% [35, 36]. There have been no nationwide surveys in India but the seroprevalence rate ranges from 43 [37] to 70% [38].

### Diagnosis

Systematic screening of Parvovirus in low risk pregnancies is currently not recommended [39]. Investigation of Parvovirus B19 is recommended as part of the standard workup for fetal hydrops or IUD [40]. Also, if a pregnant woman is exposed to Parvovirus infection or develops signs and symptoms suggestive Parvovirus infection, it should be determined whether she is immune through testing for IgG and IgM antibodies. IgM antibodies usually appear 10–12 days after inoculation and may persist up to 6 months. IgG antibodies usually appear few days after IgM antibodies and persist for several decades or even lifelong. Presence of IgG with absence of IgM suggests immunity. As a principle as explained in case of Toxoplasmosis, in cases of IgM positive but IgG negative cases, repeat blood testing should be requested after 2–3 weeks.

### *Treponema pallidum*

Syphilis, is also included in the extended group of TORCH infections. The disease is caused by a delicate cork screw shaped highly motile spirochete *Treponema pallidum*. It is mainly a sexually transmitted disease but can be transmitted transplacentally [41]. Children with congenital syphilis can have hepatosplenomegaly, snuffles, lymphadenopathy, mucocutaneous lesions, pneumonia, osteochondritis and pseudo-paralysis. As per the WHO data, 2 million pregnancies are infected annually. Infection of pregnant women results in 17–40% still births, 10–23% neonatal deaths and 10–30% congenital syphilis infection [42, 43].

### Diagnosis

The diagnosis can be made by VDRL, TPHA or ELISA tests done on mother's blood or by dark field microscopic examination of the exudates from the lesion on the genitalia or in the CSF and indirectly by serological tests [44].

## Conclusions

The antenatal diagnosis of TORCH group of infections is very important for minimizing or preventing the devastating and long-lasting ill-effects on the newborn.

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