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TORCH infections in pregnancy: Clinical laboratory and the need for a national standard

Infecciones TORCH en la gestación: Laboratorio clínico y la necesidad de una norma nacional

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ABSTRACT

Certain microorganisms grouped under the acronym TORCH - toxoplasma, other agents, rubella, cytomegalovirus and herpes simplex - very dissimilar in their taxonomy, morphology and pathogenesis, have the common characteristic of causing infections in pregnant women who can transmit them vertically, being potentially serious for the fetus and newborn. Therefore, it is essential to timely define the diagnosis through laboratory tests. However, in Peru, there is a lack of a national standard to determine the incidence and prevalence of these pathologies, to measure their magnitude and to take appropriate public health measures. The aim of this article is to disseminate the appropriate interpretation of commonly used tests and justify the design of a standard.

Key words: Pregnancy complications, infections, Congenital and neonatal diseases infection, Toxoplasmosis, congenital, Diagnosis, Morbidity

RESUMEN

Ciertos microorganismos agrupados en el acrónimo TORCH –toxoplasma, otros agentes, rubeola, citomegalovirus y herpes simple- muy disimiles en su taxonomía, morfología y patogenia, tienen como característica común causar infecciones en las gestantes quienes las pueden transmitir verticalmente, siendo potencialmente graves para el feto y el recién nacido. Por tanto, es indispensable definir oportunamente el diagnostico mediante ensayos de laboratorio. Sin embargo, en el Perú se carece de una norma nacional que permita evidenciar la incidencia y prevalencia de estas patologías, dimensionar su magnitud y tomar las medidas adecuadas de salud pública. El objetivo de este artículo es difundir la apropiada interpretación de las pruebas de uso común y justificar el diseño de una norma.

Palabras clave. Complicaciones infecciosas del embarazo, Enfermedades neonatales congénitas, Toxoplasmosis congénita, Diagnóstico, Morbilidad

Introduction

The neonate with a transplacentally acquired infection during pregnancy is a carrier of a congenital infection, which can potentially result in miscarriage, fetal stillbirth, intrauterine growth restriction or asymptomatic infection that may develop into a chronic postnatal process[1].

In 1971, Andreas Nahmias[2] defined such infections as being grouped under the acronym TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus (CMV) and herpes simplex virus (HSV)[3-5] (Table 1), which is universally used to characterize the clinical picture suffered by the fetus or newborn (NB) and which is compatible with a congenital infection caused by these microorganisms[6].

A major cause of high-risk pregnancy is this cluster of maternal infections, which often goes undetected if not actively sought. Early diagnosis of maternal disease and fetal monitoring once disease is recognized is vital[7,8]. The severity of these infections depends on the week of gestation, the immune status of the pregnant woman and the virulence of the infectious agent[9]. Seroprevalence in pregnant women can vary widely in different parts of the world[6,10].

Table 1. Microorganisms that are considered within TORCH infections. Source: Miranda-Barrios J, Sánchez-García L, Pellicer-Martínez A. Congenital infections (TORCH and parvovirus B19). Pediatr Integral. 2023;XXVII(7):364–73.

Micro-organisms that are part of TORCH
Toxoplasma gondii
Others • Varicella zoster • Parvovirus B19 • Human immunodeficiency virus (HIV) • Enterovirus • Hepatitis B virus (HBV) • Hepatitis C virus (HCV) • *Mycobacterium tuberculosis* • Zika virus • Trypanosoma cruzi (Chagas disease) • *Plasmodium* (malaria)
Rubella
Cytomegalovirus (CMV)
Herpes simplex type 1 (HSV-I) and type 2 (HSV-2)

In Peru, there are no multicenter studies, only a few circumscribed investigations[11-14] that do not give an idea of the national incidence and prevalence of these infections. Nor is there a technical health standard requiring early diagnosis. As a result, an undetermined number of pregnant women go undiagnosed, as do the etiology of fetal deaths and the morbidity of newborns related to these pathologies.

There is evidence that in certain Latin American countries some of the TORCH infections are significantly present[15-21], so specific protocols have been developed[7,16,18].

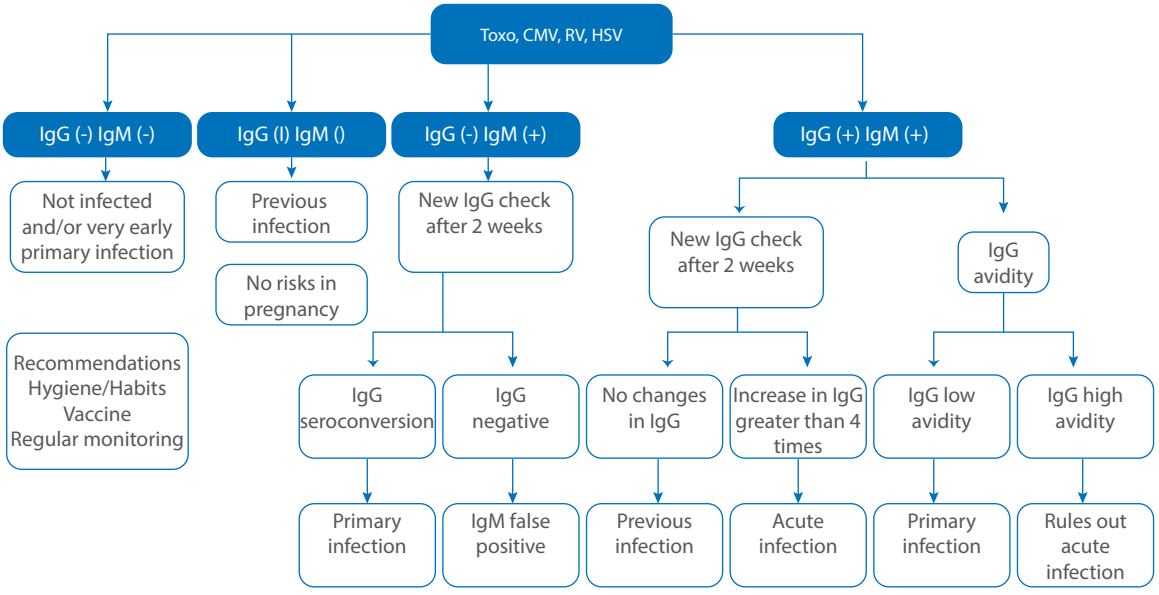
Clinical laboratory essays

These infections cannot be diagnosed on clinical grounds alone. They require various laboratory tests for identification and hazard estimation. The most frequently used are enzyme-linked immunosorbent assay (ELISA) and chemiluminescence. Polymerase chain reaction (PCR), immunofluorescence assays and immunoblot[10] are also used in certain circumstances. In recent years, rapid tests have been introduced, the most commonly used method being chromatography, which qualitatively detects immunoglobulins M and G (IgM and IgG) specific against these micro-organisms. Given the wide variety of laboratory procedures, precise knowledge of their interpretation and their validation by a reference center[7] - external quality control - is important.

The various pathologies that make up TORCH present peculiarities with regard to the ordering and interpretation of laboratory tests. However, in a generic way, the algorithm presented in Figure 1 can be useful, which corresponds to the screening of pregnant women who are initially requested to detect IgM and IgG.

In neonates, the detection of IgM and IgA is generally important to establish the presence of an active acute infection, with all the risks that this implies[7]. However, the definitive diagnosis de-

Figure 1. Algorithm for the detection in pregnant women of infection by the microorganisms that make up TORCH. Source: The importance of TORCH detection in pregnancy. Wiener Laboratories SAIC, Buenos Aires, Argentina. Published on October 31, 2023. Available at: https://www.wiener-lab.com/es-PE/new/173/



pends not only on the evolution of IgM, but also on certain microbiological and molecular biology assays and ultrasound studies, the order and interpretation of which differ according to each micro-organism, as detailed below[7].

1. **Toxoplasma**

Toxoplasma gondii, an intracellular protozoan parasite, is the etiological agent of the world's most common zoonosis[7], spread by infected food or water and undercooked meat[8]. It can infest all warm-blooded animals, including humans[7]. Seroprevalence is estimated to be around 30%[23], with 1 congenital infection occurring per 1,000 births, although this is variable, depending on the age of the pregnant woman, geographical location, hygienic conditions, living habits, nutritional status and contact with certain animals, particularly cats[7].

The fetus becomes infected during the maternal parasitemia phase, which only occurs in primary infection[24]. The danger and magnitude of congenital infection is dependent on the time of gestation at which the disease develops. The vertical transmission rate in the first three months is 7%, increases to 24% in the second trimester and fluctuates between 60% and 81% in the last three months[23]. The sequela of acute fetal infection is almost non-existent when it occurs 3 months or more before conception[9]. The interaction of *T. gondii* with the placental barrier is still poorly understood[23].

1.1. **Diagnostic tests in pregnant women**

Maternal infection is initially diagnosed by ELISA and immunofluorescence assay (ELFA), both of which detect specific IgM and IgG[25]. Both show seroconversion or a threefold or greater increase in IgG in pregnancy between two samples taken at 2–4-week intervals[24,26].

IgM appears first, usually within 1 week of infection, the titer increases up to 1-3 months, then decreases and becomes negative after 9 months, eventually becoming negative[7]. The rate of decline is variable[25]. Less than one third of the population shows sustained IgM titers for 2 or more years[7]. Consequently, the finding of IgM in pregnant women does not always imply acute infection[7]. For this, it is necessary to perform IgG avidity testing and IgA determination, or to draw another sample for IgG detection after 2-4 weeks, to see if marked differences in antibody titer occur, which would confirm an acute infection[7].

The kinetics of IgA production is similar to that of IgM, reaching a later peak and persisting for 6-7 months after the first infection[7]. In some cases, it lasts longer than 1 year or in a few acute infections it is undetectable and should be tested in conjunction with avidity testing[7]. Immunological tests are not useful to rule out infection in early pregnancy, when the diagnosis occurs after the third month and a sample is not available[7].

IgG begins to be detected as early as 2 weeks after infection[7,25], peaks at 3 months and remains stable for 6 months[7]. After 1 year, it starts to decrease slowly until it reaches its lowest level which persists for life[7,25], due to the permanence of latent cysts in the infected person[7]. High IgG levels after the fifth month of pregnancy are related to immunological memory[27].

The absence of IgG does not fully exclude the diagnosis in immunocompromised pregnant women, where the picture is shown as reactivation of a latent infection[25].

Routine IgG screening should be performed in all pregnant women during the first three months and, if negative, primary preventive measures should be taken[7]. A positive result may be due to infection prior to pregnancy, which is corroborated when IgM is negative, meaning that there is no risk of fetal infection[7].

IgG avidity tests help discriminate recent infection[28], document the time course in a single sample, but also do not provide definitive results[26,28]. Such assays are based on measuring the strength or affinity of antigen-antibody complex binding. Low affinity IgG is produced in the first months of infection and increases with time, but this progression can be modified by the application of specific treatment[29].

During the assay, the antigen-antibody complex is exposed to reagents that dissociate the *Toxoplasma gondii*-specific IgG from its antigen[25,29]. Three factors determine the stability of this complex: the antibody-epitope affinity, the values of the two components, and the structural

order of the interacting fractions[30]. These tests are usually carried out by ELISA[30].

High avidity IgG appears 12-16 weeks after infection[7]. Their presence in the first three months of pregnancy indicates that it occurred before pregnancy and there is no danger to the fetus[7]. The interpretation of IgG avidity tests depends on the reagent used, which must include information on the specific criteria involved. Ramirez-Barrios et al. propose the interpretation shown in Table 2[26].

Prenatal diagnosis of fetal infection is mandatory when serological results in the pregnant woman indicate infection immediately prior to or during pregnancy or when there is ultrasound certainty of fetal infection[7].

1.2. **Perinatal diagnostic testing**

The diagnosis of fetal infection is based on typing of the micro-organism and/or the specific immune response[7]. Replication of a deoxyribonucleic acid (DNA) sequence by PCR in amniotic fluid (AF) from 18 weeks of pregnancy has been shown to be faster and safer than other methods[7,28,31]. Its sensitivity, specificity and positive predictive value are 100%[20]. However, a negative result does not exclude infection[7]. Amniocentesis should be performed 4 weeks after the estimated date of acute gestational infection[7,31]. In the NB, the serological diagnostic criteria for congenital toxoplasmosis (CT) are[16]:

- IgG persistence after the first year of age.
- Positive IgG and IgM and/or IgA.
- Positive PCR in LA, blood, cerebrospinal fluid (CSF) and urine.
- IgG positive and IgM and IgA negative neonatal antibodies with serological evidence of acute maternal infection during pregnancy and presence of clinical manifestations suggestive of CT.

Up to 70% of neonates infected in the first three months of pregnancy may not have delectable IgM and IgA in their blood, so they should be monitored serologically for 12 months[7]. Absence of IgG at this stage of life excludes infection[7]. After delivery, PCR can be performed on the placenta, which has a specificity of 97%, but only signifies infection of this organ, not necessarily of the NB[7]. Pathological analysis of the placenta is not very sensitive and is not recommended[7].

Table 2. Interpretation of the Ig G avidity test in *Toxoplasma gondii* infection. Source: Miranda-Barrios J, Sánchez-García L, Pellicer-Martínez A. Congenital infections (TORCH and parvovirus B19). Pediatr Integral. 2023;XXVII(7):364–73.

Test result	Interpretation
When it is greater than 30%	It is considered a high avidity; therefore it is a past or chronic infection (greater than 3-4 months)
When it is less than 20%	It is considered a low avidity; it is an acute infection (less than 3-4 months)
When it ranges between 20 to 30%	It is considered a medium avidity; the result is indeterminate for an acute infection

When specific IgA or IgM are not found, PCR in blood, urine and CSF of the NB can be used as a diagnostic adjunct to serology[7]. They have adequate specificity and low sensitivity[7]. A positive result corroborates infection, but a negative result does not eliminate it and requires serological follow-up[7,31].

2. **Rubella**

Rubella is transmitted from person to person and during pregnancy by placental transfer[8]; the only known reservoir is man. It is a mild or asymptomatic infection in children and adults, but when it crosses the placenta it can cause miscarriage, fetal death or severe congenital pathologies, including hearing impairment, cataracts and heart defects, collectively known as congenital rubella syndrome[8]. The World Health Organization (WHO) promotes global vaccination programs[9]. However, seropositivity remains high in some countries.

2.1. **Diagnostic tests in the pregnant woman**

Serological testing for IgM and IgG should be performed in the pregnant woman[30]. The former is positive 1-3 days after the onset of the rash and persists for 2-3 months[30]. IgG is present from the second week after the rash[7]. Its peak titer changes from person to person; a high IgG titer is not a reliable marker of current primary infection; the absence of IgA may help to exclude it[30].

If IgM and IgG are negative, a second sample is required three weeks after infection[7]. When the study is performed more than two weeks after the onset of rash, it is recommended to complement it with the IgG avidity test[7].

Diagnosis is based on a significant increase in IgG in two blood samples drawn within 2-3 weeks[7], which becomes conclusive when the increase is 4 times the initial titer[32]. Studies should include nasopharyngeal aspirate (NPA) for virus isolation and genotyping[32], to be processed only when confirmed by serology[7].

The lgG produced at primary infection have a low avidity. Those synthesized more than 3 months later have a high avidity which is only achieved after the B-lymphocyte clone producing these antibodies has been selected as their producer. This selection starts 6-10 weeks after infection. An avidity of less than 25% indicates that the antibodies are no more than three months old[30].

After vaccination, the kinetics of the antibodies change[30]. IgM titers remain for years usually low and constant, which is not the case in natural infection[30]. After vaccination, avidity occurs more slowly than in natural infection[30].

2.2. **Perinatal diagnostic tests**

Intrauterine fetal infection is confirmed by:

- The finding of IgM in fetal blood, the highest sensitivity of which occurs after 22 weeks[26] or by evidence of persistent IgG between 6 and 12 months of life[7]. When fetal IgM is positive, a maternal serum sample is taken after delivery for IgG testing[7].
- Virus detection in chorionic villi[26].
- Detection of viral ribonucleic acid (RNA) by PCR in AF[24,26].

In addition, PCR can be performed in NPA, urine, cerebrospinal fluid (CSF) and blood up to 12 months of age[7].

3. **Cytomegalovirus (CMV)**

Humans are the reservoir hosts of CMV and are infected, as are pregnant women, by direct contact with the saliva, urine and genital secretions of infected subjects[8]. Socio-economic status, living circumstances, cultural and nutritional habits and hygienic conditions are predisposing factors in CMV seropositivity[9].

The vertical transmission rate is less than 1%. Antiviral treatment is not recommended for pregnant women, mainly because there is no drug that can reduce transmission to the fetus[9].

3.1. **Diagnostic tests in pregnant women**

Due to the lack of effective therapy to prevent congenital infection, there is no unanimity on universal screening for CMV during pregnancy[7,26]. Even in some nations, therapeutic abortion is offered when infection is evident[7]. Antibody detection is mainly by ELISA[33], with seroconversion being the most reliable way to diagnose primary infection in pregnancy[30].

IgM is found in less than 30% of women with primary infection[7] and its positive predictive value varies between 15% and 40%, depending on whether screening is general or targeted[34]. It is found within 2 weeks of the onset of symptoms[33] and remains for up to 12 months after primary infection[7], which makes it impossible to assert that its detection is synonymous with recent primary infection[30], but may mean[33]:

- Recent infection,
- Reactivation of an infection acquired in the past,
- False positive.

Detection of IgG may indicate pre-pregnancy exposure, reinfection with a different strain of CMV or reactivation of latent virus during pregnancy[7].

The IgG avidity assay helps to recognize primary infection in pregnant women[7]. In such a case, the antibodies are of low avidity, indicating an infection acquired within the last 3-4 months; high avidity IgG is only found after 2-4 months[33]. This assay, usually performed by ELISA, has the same theoretical underpinning as that described for Toxoplasma gondii infection and its interpretation depends on the reagent used, so each insert must incorporate the corresponding specific criteria. Gonzales-Garcia et al[35] propose the

values shown in Table 3. This avidity test should be incorporated into screening algorithms for pregnant women[35].

Although these assays are not suitable for detecting infections in immunocompromised pregnant women, IgG levels guide management when there is a risk of reactivation of infection[33].

3.2. **Perinatal diagnostic tests**

From 19-20 weeks, the fetus begins to excrete urine into the bladder[7]. At least 7 weeks after the presumed maternal infection must elapse before diagnostic tests can be performed[7,26]. Amniocentesis is recommended from 21 weeks of gestation[7,26], with detection of viral DNA by PCR being the preferred procedure due to its high sensitivity (90-98%) and specificity (92-98%) [7,26]. This should be complemented by serial ultrasound monitoring for evidence of fetal infection[7].

Detection of CMV in the NB can also be performed by accelerated cell culture - shell vial technique - from urine and saliva specimens, which contain high and constant concentrations[7]. Samples are taken in the first 2-3 weeks of life, as virus excretion may reflect infection acquired after birth - birth canal or breast milk[7].

Because viremia is variable, blood PCR can be more often false negative[26]. In urine[26] or liquid and dry saliva samples, this procedure has a sensitivity of more than 97% and a specificity of 99.9% compared to saliva and urine culture[7] and should be performed up to 3 weeks of age.

4. **Herpes simplex virus (HSV)**

There are two serotypes of HSV which cause the most common sexually transmitted viral disease in the world[8]. Type 1 (HSV-1) is usually transmitted non-sexually during childhood, while type 2 (HSV-2) is always transmitted sexually and is the main cause of genital herpes[8]. The infection remains asymptomatic in more than 75% of primary genital cases. However, in newborns it is a significant cause of morbidity and mortality and may cause spontaneous abortion, prematurity or congenital herpes (8).

The estimated incidence of neonatal infection is highly variable, ranging from 3 to 30 x 100,000 live births. It is believed to be globally responsible for up to 3% of infections in pregnant women[23]. Epidemiology and clinical expression have changed. HSV-1 has overtaken HSV-2 as the most frequent viral agent in neonatal infection, consistent with the increased cutaneous involvement compared to earlier times when central nervous system (CNS)-associated semiology or the disseminated form prevailed[26]. Most neonatal disease happen when the primary infection in the pregnant woman occurs late in pregnancy, close to delivery and before maternal IgG increases sufficiently to protect the fetus[23].

Table 3. Interpretation of the IgG avidity test in cytomegalovirus (CMV) infection. Source: Gonzales-García C, Reyes-Méndez M, Ortega-Pierres L, Rodríguez-Sánchez A, Sandoval-Guido V, Sereno-Colo J. Seroprevalence and detection of primary cytomegalovirus infection by IgG avidity test in the first trimester of pregnancy. Salud Pública de México. 2014;56(6):619-24.

Test result	Interpretation
When it is greater than 60%	It is considered a high avidity; therefore it is a past or chronic infection (greater than 3-4 months)
When it is less than 50%	It is considered a low avidity; it is an acute infection (less than 3-4 months)
When it ranges between 50-59.9%	It is considered a gray area; the result is indeterminate for an acute infection

4.1. **Diagnostic tests in pregnant women**

Serological assays are usually not advisable in the diagnosis of maternal infections[7]. Cross-reactions between HSV-1 and HSV-2 often occur, IgM appears late, and persistence of IgG for more than 6-12 months may corroborate infection[24]. These assays are only used when microbiological tests are negative and there is a high suspicion of infection[26], with ELISA being the most frequently used technique, detecting IgM and IgG. Only seroconversion allows the diagnosis of maternal primary infection to be made. Hence the need for two sera two to three weeks apart[36].

4.2. **Perinatal diagnostic tests**

Viral culture is the most reliable method for the diagnosis of neonatal infection[24]. However, detection of viral DNA by PCR is an acceptable and frequently used technique[24]. Before starting treatment of a neonate with suspected infection, it is advisable to swab the oral cavity, nasopharynx, conjunctiva and anus, and to take samples of skin vesicles, CSF and blood for PCR processing[7].

Because increased alanine aminotransferase (ALT) is associated with an increased mortality rate, its measurement is recommended[7]. CSF CRP is the gold standard for the diagnosis of HSV encephalitis. However, it should be noted that during the first three days the yield is only 70% and increases to 100% if the sample is obtained between the third and fifth day of evolution[7]. It is advisable to re-run the test if it was negative during the first three days[7].

Blood PCR can be effective in diagnosing neonatal infection, particularly in the absence of skin lesions[7]. Regardless of clinical classification, the sample is positive in most infected newborns[7]. Consequently, it should not be used to establish the severity of disease or the appropriate duration of treatment[7].

Blood PCR positivity may persist throughout the course of antiviral therapy. Its clinical significance is uncertain[7]. Serial PCRs are not currently advised for monitoring response to therapy[7].

Discussion

The seroprevalence of TORCH infectious diseases in pregnant women fluctuates considerably. Their diagnosis depends on various laboratory tests, the reliability of which is related to the internal and external quality controls instituted in each facility, and to the knowledge of their timely indication and correct interpretation by the treating physicians. In Peru, there is no objective evidence of the incidence and prevalence of these infections[37]. It is left to the discretion of each physician to order the tests for the corresponding diagnosis. This means that many cases may go undetected, with serious repercussions for pregnant women and newborns.

Congenital TORCH infections remain a global neonatal and child health concern; it is crucial to recognize and treat them to prevent long-term sequelae. Universal vaccination is the most effective means of prevention. Implementation of hygiene measures is also essential to prevent them and promote health.

There is no national protocol in Peru that organizes the above criteria. Only a guide for the diagnosis and treatment of congenital toxoplasmosis has been found, which was outlined for use at the Instituto Nacional Materno Perinatal (INMP)[31]. In addition, in general, governmental evaluation of the quality of reagents circulating on the market is mainly documentary. And in the few cases in which procedures are developed to determine sensitivity, specificity and other parameters, their results are not binding with regard to their continued commercialization.

The national protocol should primarily focus on diagnosis in the pregnant woman, which is the reasonable way to prevent morbidity and mortality in the fetus and/or NB. When such diagnosis is performed on the product of conception after birth, it usually only allows for documentation of the damage caused.

In countries where there is a standard for the diagnosis of one, several or all of these infections, its design varies, from being generalized and obligatory for all pregnant women to others indicating inclusion criteria to study only those pregnant women who meet them or choosing one of the components of TORCH to investigate it specifically in all or in a group of pregnant women.

In Peru, a technical consensus of experts will be required, either from a highly complex health facility or from the Ministry of Health, to define the protocol that best meets the needs of public health, in order to unify the criteria and procedures for diagnosis, treatment and follow-up of these infections and thus have objective evidence of their incidence and prevalence, while seeking to reduce their deleterious effects on the mother and the product of conception.

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