

## REVIEW ARTICLE

## Congenital infections of low frequency in newborns: some relevant aspects

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### ABSTRACT

This article aims to update a previous study involving approximately 13 diseases acquired transplacentally by newborns. We did not perform a systematized and detailed description of each condition in this review, but rather we mention some facts that will enable the general practitioner and pediatrician to keep these in mind, using some highlights on the demonstration of the physiopathogeny, clinical or laboratory tests and, even more so, with the probability or certainty that the mother developed any of the diseases during pregnancy. These 13 diseases were selected because 1) some appear in a low frequency worldwide, 2) there are no reported cases in the national literature, or 3) the number of women in Mexico of childbearing age experiencing them. It prompts us to think that, based on the frequency of congenital transmission, there should be more cases than what is actually reported.

**Key words:** congenital infections, vertical infections, transplacental infections.

### INTRODUCTION

Vertical infections are defined as those acquired by a newborn as a result of maternal infection during gestation. These infections can be transmitted transplacentally by an ascending path from the vagina during delivery or after birth.<sup>1</sup> Pathogens able to be transmitted transplacentally are comprised of 25-30 viruses, 10-16 bacteria, 3-5 parasites, etc. When the newborn is infected during delivery, transmittable pathogens are comprised of 8-10 viruses, 30-40 bacteria, 10-14 parasites, et al. Ambiguity regarding the actual number of transmittable pathogens is as a result of the scientific literature reporting disagreement on the possibility that some pathogens are transmitted transplacentally or because they include those transmitted during childbirth.<sup>2</sup>

Of stillbirths, in developed countries 10-25% are directly associated with infection. In developing countries there are higher percentages of stillborns, and infections represent one of the leading associated factors. Fetal deaths may be associated with direct fetal infection, placental damage or a severe illness experienced by the mother. A large number of microorganisms have been associated with those deaths including bacteria, viruses and protozoa. The most frequent microorganisms involved in an ascending path infection, either before or after membrane rupture, are *Escherichia coli*, Group B *Streptococci*, and *Ureaplasma urolyticum*. However, *Treponema pallidum* has been associated with up to 50% of deaths in areas where syphilis is prevalent. Malaria has been regarded as a frequent cause of infection in women who become infected for the first time during pregnancy. The leading causes with viral etiology are parvovirus and coxsackievirus although there may be others yet reported. *Toxoplasma gondii*, *Listeria monocytogenes*, and organisms causing leptospirosis, Q fever and Lyme disease have also been associated with fetal death.<sup>3</sup>

Examples of potential microorganisms that transmit infections from a mother to the fetus are given by herpes viruses. Cytomegalovirus (CMV) has a high probability of maternal/fetal transmission either transplacentally, transcervically or after birth.<sup>4</sup> Herpes simplex 1 and 2 are less likely to be transmitted transplacentally rather than

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transcervically and even have a lower transmission rate after birth (Table 1). A similar situation occurs with varicella-zoster virus, whereas herpes virus 6 reports a lower transmission rate. There is no evidence that other viruses have a maternal/fetal mode of transmission (although they potentially can).<sup>5</sup>

Herpes viruses are the second leading cause of viral infections in humans. Herpes simplex 1 and 2 and varicella-zoster virus produce neurotropic infections such as cutaneous herpes, genital herpes and chicken pox; lymphotropic infections are caused by CMV, HHV-6, HHV-7 and Epstein-Barr virus and are able to produce lymphoma, carcinoma and congenital alterations as well as other conditions affecting immunocompromised patients.<sup>6</sup>

In vertical infections, 80-90% of cases do not present clinical signs at birth or they may appear days after delivery, whereas 10-20% of cases may present clear symptoms such as hepatomegaly, jaundice, adenopathy, petechiae, vesicles, maculopapular exanthema, hydrocephalus, microcephaly, encephalitis, myocarditis, malformations and chorioretinitis, to name the most common. Other signs will appear depending on the type of infection.<sup>2</sup>

Laboratory exams used to establish diagnosis are usually the same tests used to diagnose infectious diseases; however, vertical infections with viral etiology would ideally require pathogen identification, although this would be expensive and of little help for immediate decision-making. Therefore, certain methods prevail in daily practice such as immunofluorescence using monoclonal antibodies, polymerase chain reaction for viral DNA/RNA, agglutination inhibition, ELISA for IgG and IgM, to name the most frequent. To diagnose infections produced by parasites, bacteria, fungi and others, the chief method

is pathogen identification with complementary serological studies appropriate for each case.<sup>2</sup>

The purpose of this article is to raise awareness for pediatricians in regard to 13 diseases acquired by newborns transplacentally and documented in the recent scientific literature, although some diseases may also be acquired by various pathways.

I will not provide a detailed and systematic description for each disease, but I will highlight relevant facts that enable general physicians and pediatricians to identify certain aspects of their pathophysiology, clinical manifestations and laboratory tests so that they may keep these in mind, especially when they are aware that the mother developed a specific disease during pregnancy. I have chosen these 13 diseases because some have a low frequency worldwide and because there are no reported cases in Mexico. Others were chosen because the number of fertile women who experience them in Mexico suggests that these diseases should have a greater prevalence in newborns than what is reported.

#### Herpesvirus 6 and 7

Since Yamanishi et al. described in 1988 that herpes virus-6 and, in a much lower proportion, herpes virus-7 were responsible for sudden exanthema (roseola infantum), research on these herpes viruses has increased. Today we know herpes virus-6 is acquired by most children prior to the age of 2 years<sup>7</sup> and herpes virus-7 is acquired at a later age. Of children <3 years of age who arrive at emergency services with a nonspecific fever, ~10% present HHV-6.<sup>8</sup> Ten years ago it was suggested that vertical transmission of HHV-6 was possible and the virus was later identified in peripheral blood and in

**Table 1.** Potential ability of vertical transmission paths associated with herpes viruses

<i>Herpesvirus</i>	<i>Transplacental</i>	<i>During delivery</i>	<i>Postnatal</i>
Cytomegalovirus	+++	+++	+++
Varicella-zoster virus	+	++	++
HHV-6	+	+	+
Epstein-Barr virus	+/-	+/-	UK
Kaposi's sarcoma herpesvirus	+/-	+/-	+
HHV-7	UK	UK	UK

UK, unknown; +/-, reasonable potential but not supported; +, rare but described; ++, frequent; +++, common infection.

the mother's genital tract plus the fact that transplacental infection was demonstrated. HHV-6 represents an infection risk between 1 and 1.6% for newborns.<sup>6,9,10</sup> It is worth highlighting that HHV-7 has not been associated with transplacental infection even though it shares several epidemiological and biological characteristics with HHV-6. CMV also shares genetic characteristics with HHV-6 and has been considered to be the leading cause of hypacusis and sensorineural hearing loss in children with congenital infection, in addition to a number of cerebral palsies and cognitive disorders. Because of the similarities of CMV with HHV-6, it has potential to become an important public health problem.<sup>11</sup>

It has been suggested that HHV-6 transmission results after reactivation of a latent infection in the mother because this mechanism usually leads to CMV infection. HHV-6 viral replication has not been demonstrated in newborns until 2 or 3 years ago; however, CMV replication can extend for months or even years after birth.<sup>12,13</sup> It has recently been demonstrated in six children who acquired HHV-6 transplacentally by analyzing blood samples from umbilical cord, peripheral blood, saliva, urine and hair that HHV-6 DNA was compatible with samples analyzed from their parents' hair. Of parents, six mothers and none of the fathers presented the same DNA variant found in their offspring, which suggests viral replication is possible and may be one of the causes of congenital infection.<sup>14</sup> It has recently also been demonstrated that HHV-6 is found with a higher prevalence in newborns from mothers positive for human immunodeficiency virus (HIV) (3.2%), whereas the prevalence in newborns from HIV-negative mothers is 1.6%.<sup>15</sup> Regarding HHV-7, it has been demonstrated that DNA is found more frequently in peripheral blood of pregnant women (66.9%) compared with a 22.2% prevalence of HHV-6 cases. Vaginal discharge shows a frequency of 3% for HHV-7 and 7.5% for HHV-6. It has also been identified that in cervical secretions HHV-6 associates with DNA taken from the mother's peripheral blood samples, which implies there was active placental infection associated with congenital infection from HHV-6.<sup>16</sup> Because it is difficult to suspect an infection from these herpes virus variants and no clinical data have been identified at the time, we will need to wait until more information about the natural history of the disease arises in order to be able to identify the consequences of transplacental infection.

### Herpesvirus 1 and 2

Neonatal herpes simplex is a serious condition and represents the most important complication associated with genital herpes, being one of the most common and severe congenital and perinatal infections. Prevention possibilities have increased recently with advances in diagnosis and treatment. It is worth noting that neonatal herpes simplex is not reported to U.S. healthcare authorities in several states even though the disease complies with every requisite to be reported:

1. Its incidence exceeds that of comparable diseases.
2. It is epidemiologically unstable.
3. It is a serious condition.
4. There are important social and economic costs associated with it, both directly and indirectly.
5. They produce concern for persons who are at risk of developing the disease.
6. It is possible to take preventive measures through public health care programs.
7. Public healthcare actions can be performed, supported by case notifications and reported findings.

These should be sufficient reasons to report these cases to public health authorities. Unfortunately, this situation also occurs in Mexico.<sup>17</sup>

There are no statistics in Mexico on the rate of vertical infection; however, there are an average of 1,500 to 2,000 cases of neonatal herpes simplex in the U.S. every year.<sup>18</sup> It has been reported that maternal antibodies for HSV-1 represent a small to nil protection against neonatal infection by HSV-2. During reactivation, HSV-1 seems to be more easily transmitted to newborns than HSV-2, which has raised concerns because of the increasing frequency of HSV-1 genital infections.<sup>19</sup>

There are three clinical presentation varieties for transplacental infections:

- 1) Localized in skin, eyes and mouth with a mortality rate between 0.1 and 0.5% (depending on the series)
- 2) Localized in the central nervous system and may be accompanied by lesions on skin, eyes and mouth, with an estimated mortality rate ~15%
- 3) Disseminated disease with a mortality rate between 55 and 80%<sup>20</sup>

Of newborns who acquire vertical infection, 55% come from mothers with HSV-1 or HSV-2 primary infection. Infection after a nonprimary episode represents 33% of cases, whereas relapsing infection accounts for 3% of affected newborns.<sup>20</sup> A primary infection acquired during the second or the third trimester of pregnancy increases the risk of premature delivery as well as fetal infection. Polymerase chain reaction and hybridization methods are best suited for diagnosis.

Primary and nonprimary infections report 80% virus identification in ulcers, which decreases to 40% when there are relapsing ulcers. Caesarean delivery should be carried out as soon as possible when a maternal primary infection is detected and there is membrane rupture, near-to-end gestation or when there are active lesions or intense vulvar pain with a burning sensation.<sup>20</sup>

### Dengue Fever

Dengue fever is the viral disease transmitted by mosquitoes with the highest impact on worldwide public health. It can be found in ~100 countries including Mexico and belongs to the flavivirus group of viruses, which are associated with yellow fever, Venezuelan encephalitis, Japanese encephalitis and West Nile virus infection. Persons infected by dengue are frequently asymptomatic, but they may develop a disease resembling influenza or a more severe condition with some fatal cases associated with hemorrhage and shock.

Pregnant women living in a country where dengue is endemic, or during an epidemic, should be tested for the disease and fetal infection should be suspected when the patient presents fever, myalgia and/or bleeding. This calls for close surveillance of both mother and unborn child.<sup>21,22</sup> The first five cases were reported in Tahiti in 1989 and, after that, 10 more cases have been reported [Thailand (6), Malaysia (2), France (2)].<sup>23</sup> A review of all 17 cases revealed that all patients presented fever and thrombocytopenia, 14 had hepatomegaly, two had erythematous rash and two had an increase in transaminases. All newborns ( $n = 17$ ) had thrombocytopenia and, of these, 13 had platelet counts  $<30,000/\text{mm}^3$  and two presented only minor gastric bleeding.<sup>23</sup>

Transplacental infection is more frequent when the mother presents a secondary infection, possibly because there is a higher viral load in the secondary infection than in the primary. A recent systematic review of pregnant

women with dengue found 19 cases, 9 from case series and two comparative studies. Case reports showed 44% with cesarean delivery and 12% with preeclampsia, eclampsia or fetal death. Case series reported a premature delivery of 16% and 12% cesarean deliveries. Vertical transmission was present in 64% of case reports and in 12.6% of case series.<sup>24</sup> Another study identified that during pregnancy dengue produced 20% premature births, 3.8% intra-uterine deaths, 7.5% fetal suffering and 5.6% transplacental infections.<sup>25</sup>

### Papillomaviruses

Papillomaviruses may be transmitted through sexual contact and there is evidence of transplacental transmission, although it was thought that newborns only acquired this disease transcervically. Transplacental transmission is supported by cases of condyloma acuminatum, laryngeal papillomatosis or anogenital lesions.<sup>26</sup> Transmission rate has been identified to be between 38% and 73%. It has been demonstrated that transmission frequency for newborns is ~40% for HPV-18 and 50% for HPV-16, whereas both serotypes were present in 30% of cases. Transplacental infection has been regarded as a frequent possibility in addition to transcervical infection because even newborns who have been delivered via cesarean section present a high rate of papillomavirus.<sup>27</sup> It has not been possible to determine if papillomavirus identification at birth causes a persistent disease or represents only a transient infection. It has been considered that even though relapsing respiratory papillomatosis has a low frequency (1 to 4/100,000 cases), it is acquired during delivery as well as transplacentally.<sup>28</sup> It has been reported that papillomavirus persists in 83% of newborns until they reach 6 months of age.<sup>29</sup> If the latter is confirmed, we should consider the possibility to establish preventive strategies such as application of a specific vaccine. A matching prevalence of mother/child papillomavirus DNA has been found in viral types available for the vaccine. This suggests that vaccination prior to pregnancy has a low efficiency for preventing vertical viral transmission.<sup>30</sup> However, another phase-3 study where papillomavirus vaccination against four strains was used in 1,796 pregnant women and 1,824 controls found no significant differences in the proportion of pregnancies that ended with live newborns, fetal deaths or spontaneous miscarriages. Of that study, 40 newborns from vaccinated mothers and 30 newborns from control group had one or

more congenital malformations. This was regarded as not statistically significant because those malformations are prevalent in the general population. The vaccine was well tolerated in pregnant women. Nevertheless, the U.S. Food and Drug Administration (FDA) has not authorized its use because it considers that results of malformation (although not statistically significant) require additional studies before accepting or rejecting the vaccine.<sup>31</sup>

### Coxsackie Virus

The role this virus plays in transplacental infection and its association with morbidity and mortality has not been sufficiently documented. Although a study suggests that maternal infection during the third trimester of pregnancy did not increase morbidity in newborns,<sup>32</sup> there are other studies where transplacental infection has been associated with significant neonatal morbidity and mortality, even producing death or long-term neurological sequelae secondary to the extent of cortical necrosis.<sup>33</sup>

Early fetal deaths have been diagnosed in symptomatic women with high virus titers in blood at the beginning of pregnancy. Coxsackie virus in amniotic fluid has been identified during amniocentesis carried out in the last trimester of pregnancy, supporting that this is the mode of transmission. Transplacental transmission cases have been documented for Coxsackie B5<sup>34</sup> and B3 viruses.<sup>35,36</sup>

In contrast with mild clinical presentations experienced by adults, newborns affected may develop a severe condition either as a result of pneumonia, myocarditis and/or meningoencephalitis. A newborn may present a clinical profile similar to septicemia with hypotension, leukopenia or leukocytosis, neutropenia, thrombocytopenia and disseminated intravascular coagulation. Central nervous system lesions are presented at all levels of gray matter but are more common in brain and are liquefaction necrosis areas where there are minimal inflammatory changes.

### Malaria

Malaria is leading cause of death worldwide associated with parasites. It reaches 120 million cases per year, which contrasts with transplacental transmission where only 300 cases have been reported in the literature to date.<sup>37</sup> Pregnant women have a probability 4-12 times higher to contract malaria than nonpregnant women and prevalence is even higher during the first pregnancy. Since 1950, 49

cases have been reported in the U.S.,<sup>38</sup> and more cases have since been reported.<sup>39</sup>

It has been estimated that a malarial infection in a pregnant woman has a transplacental transmission risk of 1-4%, reaching 13.6% in endemic areas.<sup>40</sup> Malaria can also be transmitted together with *P. vivax* and *P. falciparum* when there is chloroquine resistance during pregnancy<sup>41</sup> and even in combination with *P. falciparum* and tuberculosis.<sup>42</sup> There are documented coinfection cases of *P. vivax* and HIV in mothers who had both diseases and their placentae showed a high *Plasmodium* invasion, significantly increasing the risk of congenital infection.<sup>43</sup>

The classic clinical profile of congenital infection includes fever, anorexia, lethargy, anemia, hyperbilirubinemia, thrombocytopenia and splenomegaly. Average time of onset is 5 weeks but it may vary from birth up to 60 weeks after delivery. A review of the aforementioned 49 cases revealed that there was fever in 100% of cases and hepatosplenomegaly in 84% of cases. Bilirubin and transaminases increase as a consequence of intravascular hemolysis and hepatic congestion, which recede several days after specific therapy is initiated. Peripheral blood culture may be sufficient for diagnosis. It is highly recommended to test blood from umbilical cord and placenta. If the placenta has a high number of trophozoites, congenital infection should be suspected. Treatment of congenital infection in newborns has shown good results applying artesunate intravenously followed by oral dosages of dihydroartemisinin-piperachine.<sup>44</sup>

### Leishmaniasis

Visceral leishmaniasis during pregnancy is rare; however, it requires special care because even though there is an actual possibility of vertical transmission, there is scarce information on this subject. Because there are endemic areas in the world (including Mexico), as well as an ongoing population growth, more visceral leishmaniasis cases during pregnancy are being identified. Unfortunately, textbooks usually do not deal with this variant and publications regarding it are scarce.<sup>45</sup>

It has been considered that congenital transmission of maternal visceral leishmaniasis is almost nonexistent.<sup>46</sup> However, since 1995 and to date, 14 cases of congenital transmission have been reported.<sup>47-49</sup> Therefore, when this disease is found in a pregnant woman, close follow-up of the newborn should be carried out during the first months

of life. In cases with fever, pancytopenia and splenomegaly, further investigation is recommended to rule out this disease.

### **Tuberculosis**

Congenital tuberculosis is seldom diagnosed in countries with a low prevalence of tuberculosis. However, the increasing number of HIV cases and migration of persons from countries with a high prevalence of tuberculosis to other countries where it is almost nonexistent should be considered in order to identify a possibly larger number of cases of congenital tuberculosis.<sup>50-53</sup>

There have been 300 cases of congenital tuberculosis reported and, recently, 11 additional cases were reported in a South African area where the disease is endemic.<sup>54</sup> This is a fatal disease if undiagnosed or untreated. The most frequently affected organs during congenital/perinatal presentation are liver, lungs, and lymph nodes. Sites less frequently affected are brain, meninges, adrenal glands, internal ear and skin.<sup>55</sup> Perinatally, the disease can be acquired in utero or early after birth by contact with infected relatives (including the mother). Beitske established the congenital criteria in 1935, which was later modified by Cantwell et al. in 1994.<sup>56</sup> At least one of the following should apply:

1. Lesions during the first week of life
2. Primary hepatic complex or caseous hepatic granuloma
3. Tuberculous infection in placenta or genital tract of the mother
4. Exclude postnatal transmission from an exhaustive investigation of contacts

Clinically, newborns with congenital tuberculosis are frequently premature with low birth weight, loss of appetite and lethargy. A study carried out at the National Institute of Perinatology in Mexico City identified a morbidity of 23% in newborns from tuberculous mothers compared with 3.8% in the control group.<sup>57</sup> This morbidity presented higher rates for prematurity, fetal death and low birth weight; however, no congenital cases of tuberculosis were found, possibly because some mothers received treatment from the first trimester of pregnancy or because the sample size was small. Other common signs of congenital tuberculosis are respiratory insufficiency,

hepatomegaly, splenomegaly and lymphadenopathy. As an exception, there was a case reported in Australia for congenital tuberculosis in a child conceived by *in vitro* fertilization with one case as antecedent. Therefore, careful investigation is recommended for women who are receiving infertility treatments.<sup>58</sup>

### **Candidiasis**

Congenital cutaneous candidiasis has a very low prevalence in newborns, whether full-term or premature. Its presentation includes a generalized skin rash at birth or shortly after birth, generally without other symptoms. The rash usually is erythematous with maculae, papules or pustules.<sup>59</sup>

Milky microabscesses in placenta and umbilical cord when a newborn presents rash should raise diagnostic suspicion secondary to chorioamnionitis, which can be undetected. Incidence of vertical path infection after vaginal infection is <1% and this mechanism rarely produces chorioamnionitis from *Candida* spp.<sup>60,61</sup> Despite the high prevalence of vulvovaginitis from *Candida* spp. in pregnant women (10-35%), chorioamnionitis from *Candida* spp. has a low prevalence, which is supported by documentation of ~100 cases of transplacental candidiasis. However, because newborn presentation is generally benign, it is possible that this disease is underdiagnosed.

Chorioamnionitis from *Candida* spp. can evolve into a systemic disease in newborns, particularly when they are premature. Main risk factors are intrauterine foreign bodies, cervical cerclage or premature birth. A review of published cases reports that if children are premature (<1,000 g birth weight), they frequently present spreading of skin shedding and/or erosive dermatitis, with 67% risk of systemic infection and 40% risk of death. Newborns with >1000 g of weight have a prevalence of the above conditions of 10% and 8%, respectively.<sup>62,63</sup> In order to confirm transplacental infection, in addition to clinical data and cultures where candida has been identified, it is necessary to carry out molecular tests in the mother and the child including chromosomal karyotype and a restriction endonuclease analysis followed by pulsed-field gel electrophoresis.<sup>64</sup>

### **Syphilis**

Untreated syphilis during pregnancy (especially during early stages) may lead to fetal and neonatal deaths or

produce deafness, neurological damage and bone malformations. The disease can be prevented by detection and early treatment, at least 30 days before birth. Changes in the incidence of primary and secondary syphilis among women are concurrent with congenital syphilis. The U.S. Centers for Disease Control and Prevention carried out a study between 2003 and 2008 where, after a 14-year period of decrease, congenital syphilis in children <1 year of age increased by 23%: from 8.2 cases/100,000 live newborns in 2005 to 10.1 cases/100,000 live newborns in 2008.<sup>65</sup>

Congenital syphilis can be present when a mother with active syphilis is untreated during pregnancy or when treatment is inadequate. Symptoms in newborn are frequently subtle and nonspecific, and it has been estimated that up to 60% of affected children are asymptomatic at birth, which makes diagnosis dependent on laboratory tests. Despite decades of experience with congenital syphilis, there are still problems associated with diagnosis because of laboratory tests. The development of radioimmunoassay and polymerase chain reaction tests has increased the sensitivity and specificity for diagnosis; however, detection of specific IgM is currently the most sensitive serological test. In order to exclude or to confirm diagnosis, it is useful to carry out several tests after birth applying kinetic analysis of specific antibodies. When the disease is suspected, it is ethical to continue treatment for the newborn.<sup>66</sup>

Table 2 shows the number of cases of acquired and congenital syphilis has remained stable between the years 2000 and 2008 in Mexico. Congenital syphilis increased in 2007 and 2008 and then presented a small decrease in 2009. This is a concerning situation because it is expected that a large number of newborns also had the disease and this was undetected or misdiagnosed with other nosological entities. Any pregnant woman diagnosed with syphilis has a risk of transplacental transmission of 20 to 40%; therefore, independent of treatment received by the mother, the newborn will require specific testing on congenital infection. There are other percentages of transplacental transmission as demonstrated by a retrospective analysis (from 2003 to 2007) where 42/1,010 children born from mothers with active syphilis presented congenital syphilis diagnosed through the 19S-IgM-FTA-ABSA test. This represented a 4% prevalence and nine additional cases were identified on longitudinal follow-up. Another study carried out with 549 pregnant women with active syphilis found a transmission rate of 5.2%.<sup>67</sup> The most common

clinical data are palm and plantar desquamation, hepatosplenomegaly with or without jaundice, persistent rhinitis and lymphadenopathy.<sup>68,69</sup>

### Rubella

After the bilateral U.S./Mexico initiative of 1999, a significant reduction of acquired rubella has occurred and this has also impacted congenital infection (Table 2). However, we still did not achieve the goal to have zero cases for the year 2000 (which was also shared by PAHO),<sup>70</sup> and this goal was restated by PAHO on the Americas by the year 2010. This goal has not been achieved because there was an epidemic in Argentina, Brazil and Chile with 13,014 cases in 2007. Before this, a reduction of 98% was accomplished in the Americas (from 135,947 to 2,998 cases).<sup>71</sup>

Considering the important reduction of acquired rubella cases and the almost nil presence of congenital infection, rubella has become a disease of very low prevalence as a result of efficient vaccination campaigns carried out in Mexico (Table 2). However, we should keep in mind that there have been rubella outbreaks in South America as well as in Europe, despite good vaccination campaigns. Therefore, it was important to include this disease in this chapter. Congenital rubella can be developed in 43% of cases if a woman is infected within 26 days before conception. If infection occurs within the first 12 gestation weeks, possibilities increase to 51%, and if infection occurs between the 13<sup>th</sup> and the 26<sup>th</sup> week, then it decreases to 23%. Infection prevalence during the third trimester is infrequent and malformation risk is almost zero.

Classic manifestations of congenital rubella in newborns are as follows: ~55% deafness, 34% cataracts, microphthalmia, retinitis or glaucoma and 43% congenital cardiopathy of arterial duct or pulmonary stenosis. Other less frequent clinical manifestations are hepatomegaly, splenomegaly, jaundice, low birth weight, microcephaly, micrognathia, psychomotor retardation, encephalitis, meningitis and arthritis.<sup>72</sup> Genotypes involved in congenital rubella have been identified during the last 15 years in France (1995-2009), with 1E, 1G, 1B, 2B and 1H and with 87% of cases associated with 1E.<sup>73</sup>

### Chagas Disease

This disease is caused by *Trypanosoma cruzi* and chiefly transmitted by an insect bite (*Triatoma infestans*) as well as transfusional and transplacental paths. The latter is

**Table 2.** Ratio of new rubella cases per year and syphilis acquired by women of reproductive age (15-49 years old) and the number of children diagnosed with congenital rubella or syphilis

Report year	Acquired rubella (n)**	Congenital rubella (n)***	Acquired syphilis (n)**	Congenital syphilis (n)***
2003	240	0	1069	100
2004	106	5	1138	125
2005	81	1	1150	91
2006	17	0	1311	78
2007	23	0	1420	148
2008	18	1	1393	168
2009	0	0	1152	86

\*Epidemiological Bulletin from National Center for Epidemiological Surveillance (Secretary of Health, Mexico; 2008 and 2009).

\*\*These columns were updated using information from the female age group between 15 and 49 years old.

\*\*\*These data were updated using available information of children of both genders and, when congenital, we usually apply a <1 year-old criterion.

observed not only in endemic countries of Latin America, but it has been recorded on other continents because of population migrational patterns.<sup>74-81</sup>

It has been estimated that there are ~2 million women of childbearing age in Latin America who may transmit the parasite to their fetuses.<sup>82</sup> Other estimations indicate at least 15,000 newborns become infected with *T. cruzi* every year in Latin America and 2,000 newborns in North America.<sup>83</sup> This transmission path has increased in Europe because of migration of persons who are native of countries where the disease is endemic.<sup>84-87</sup> Prevalence of transplacental transmission of *T. cruzi* varies in Latin America. Depending on diagnostic method and epidemiological factors, prevalence can oscillate between 1 and 18.8%. For instance, it has been estimated that, in Chile, transplacental transmission in endemic zones in urban and rural populations is 6.3% and 8.9%, respectively.<sup>74</sup> In Bolivia where Chagas disease is highly endemic, 17% of pregnant women have been found to be chronically infected by *T. cruzi* and congenital transmission is presented in 5-6% of cases.<sup>88</sup>

It has been demonstrated experimentally that parasitic invasion into the placenta induces destruction and detachment of syncytiotrophoblast, selective disorganization of basal lamina and connective collagen tissue because of a possible proteolytic activity associated with the parasite.<sup>75</sup> Clinical manifestations of transplacental infection can be similar to those included in expanded TORCH, such as multisystemic alterations, hepatomegaly

and splenomegaly, jaundice, generalized edema or limb edema, neurological disorders, hemolytic anemia, thrombocytopenia, petechiae, ecchymosis and easy bleeding at venopuncture sites. Eye fundus exam reveals alterations in retina, vitreous humor and pupillary edema as well as other electrocardiographic disorders in ventricular repolarization. Cerebrospinal fluid presents in most cases a high number of proteins and a prevalence of mononuclear cells, even without neurological symptoms. Infected newborns are frequently premature and present intra-uterine growth retardation. There are important variations in infection presentation ranging from full-blown clinical profiles to the apparent absence of signs and symptoms that would elude diagnosis if not deliberately searched for.

Diagnosis is established by identifying the parasite in fresh blood (micro-Strout) or by culture and then xenodiagnosis. Other methods include indirect immunofluorescence reaction and ELISA for IgG and IgM. Polymerase chain reaction can also determine the species and group, taking samples from the mother and newborn.<sup>76</sup> Recommended treatment is nifurtimox in 8-15 mg/kg/day dosages for 60-90 days or benznidazole at 5-7 mg/kg/day dosages for 35 days. Treatment is generally well tolerated.<sup>89,90</sup>

Curing the disease in children represents a complex problem that has lead to inconsistent and controversial results. The absence of reliable methods or a gold standard to evaluate the efficiency of etiological treatment represents one of the current challenges.<sup>91,92</sup>



### Influenza

Pregnant women are one of the groups with the highest risk for contracting influenza A as well as to develop serious complications including maternal death. Transplacental infection of influenza A is a rare event<sup>93</sup> with only a few cases reported;<sup>93-95</sup> furthermore, other studies have been unable to demonstrate it.<sup>93,96</sup> Viremia during pregnancy is more intense because of the reduced immune cellular response.

During the influenza A (H1N1) pandemic in 2009, we identified the groups with the highest risk of infection and complications and these included pregnant women and children. There is one case reported of perinatal infection<sup>97</sup> that seems to be the only one reported in literature and, therefore, will be described here in detail. The mother was diagnosed with influenza A (H1N1) infection from the 2009 pandemic. The newborn was delivered through cesarean delivery at the 31<sup>st</sup> gestation week because of maternal respiratory insufficiency. The newborn weighed 1,560 g. Apgar score was 9-9 at the first and fifth minutes of life. At birth, there was a mild costal retraction with 91-95% oxygen saturation at normal environment. No other alterations were found during physical examination. Based on the mother's history, a pharyngeal sample was taken

to test for influenza A (H1N1) virus through PCR. The newborn received oseltamivir 4 mg/kg/day (6 mg/12 h). He tested positive for the virus. The newborn required supplementary oxygen and presented a creatinine increase of 1.1 mg/dL. Chest x-ray revealed minimum pulmonary infiltration. He was treated with cefotaxime because of sepsis suspicion. Oseltamivir dosage was adjusted based on glomerular filtration rate (10.5 mL/min/1.73 m<sup>2</sup> to 3 mg every 12 h until receiving 10 dosages (2 mg/kg/day). Newborn infection was confirmed using real-time reverse-transcriptase (RT) PCR from pharyngeal sample and a 4-fold increase of antibody titers against the virus through hemagglutination inhibition test. Another sample for PCR was taken at the fourth day of life and was negative. Clinical conditions evolved gradually towards healing until oxygen was removed, having a negative blood culture, decrease of serum creatinine to 0.6 mg/dL at the seventh day with a urinary output of 2-3 mL/kg/h. The patient was discharged at the 28<sup>th</sup> day of life with a weight of 2,070 g. Despite scarce reports on transplacental transmission, we should always consider its possibility when the mother develops the disease during pregnancy, especially in endemic or epidemic situations such as the event in 2009.

**Table 3.** New cases reported of transmittable diseases\* and their incidence in Mexico\*\* between 2008 and 2009 (focus on women of reproductive age: 15 to 49 years old)

Disease	Year 2008		Year 2009	
	Cases (n)	Incidence**	Cases (n)	Incidence**
Urogenital candidiasis	255,688	858.2	248,785	826.02
Chagas disease	98	0.3	81	0.27
Genital herpes	891	1.04	975	3.24
Hepatitis A	1,541	16.38	1,545	5.13
Hepatitis B	166	0.68	137	0.45
Hepatitis C	407	1.76	411	1.36
Leishmaniasis	121	0.38	91	0.30
<i>P. vivax</i> malaria	518	1.98	565	1.88
<i>P. falciparum</i> malaria	0	0.0	0	0.0
Acquired rubella	18	0.04	0	0.0
Acquired syphilis	1,393	2.78	1,152	3.82
Pulmonary tuberculosis	3,154	10.46	3,155	10.48
Meningeal tuberculosis	52	0.16	58	0.19
Other tuberculosis	799	2.56	783	2.60
Human papillomavirus	19,735	41.26	23,285	77.31
Dengue fever	9,055	28.95	42,648	141.60
Hemorrhagic dengue fever	2,322	7.04	3,488	11.55

\*Epidemiological Bulletin from National Center for Epidemiological Surveillance (Secretary of Health, Mexico; 2008 and 2009).

\*\*Incidence per 100,000 female inhabitants between 15 and 49 years old.

**Table 4.** Risk rates for fetuses in regard to transplacental infections based on medical literature

Disease	Transplacental transmission risk rate
Urogenital candidiasis	41% <sup>98</sup>
Chagas disease	Between 1% and 18.8% depending on country and endemic area. Urban and rural populations have a prevalence of 6.3% and 8.9%, respectively. <sup>74</sup> Bolivia has reported an incidence of 5% to 6%. <sup>88</sup>
Genital herpes	HHV-6 and HHV-7 from 1% to 1.6% <sup>14,16</sup>
Hepatitis A	From 2% to 15% <sup>99</sup>
Hepatitis B	From 20% to 80%, depending on mother's viral load <sup>100</sup>
Hepatitis C	11% <sup>99</sup>
Leishmaniasis	No information published
HIV	From 1% to 2% with antiretroviral therapy, cesarean delivery and avoidance of breastfeeding. Without these recommendations, it may reach 30%. <sup>101</sup>
Malaria ( <i>P. vivax</i> or <i>P. falciparum</i> )	From 1% to 4% and even 13.6% in endemic areas. <sup>40</sup>
Acquired rubella	43% when a woman becomes infected within the first 26 days prior to conception; 51% when infection occurs within the first 12 gestation weeks; 23% when infection occurs between the 13 <sup>th</sup> and the 26 <sup>th</sup> gestation weeks.
Acquired syphilis	From 20% to 40% <sup>67</sup>
Tuberculosis	16% <sup>102</sup>
Human papillomavirus	From 38% to 73%; 40% for HPV-18 and 50% for HPV-16; 30% for both serotypes. <sup>27</sup>
Dengue	64% of case reports; 12.6% in case series <sup>24</sup> and 5.6% in prospective studies. <sup>25</sup>

Table 3 shows the number of cases of diseases in Mexico between 2008 and 2009 with a potential transplacental transmission risk including infections mentioned here: HIV and hepatitis A, B and C. The purpose of these data is that by knowing the vertical transmission risk rates, we could estimate how many children may be infected transplacentally. Obviously, the number of potential cases in pregnant women is not shown; however, figures presented here suggest the number of cases may be significant each year in Mexico.

Finally, Table 4 summarizes information on vertical transplacental infection of 14 diseases. It is notable that the potential infection rate is variable, depending on available information in the literature. However, this information has been regarded useful as is because research in the national or international literature is time consuming and available reports are scarce.

In conclusion, although transplacental infections from many of the diseases presented here have a low prevalence, it is true that this may be much higher if these diseases were tested intentionally, either in endemic areas of Mexico or in the general population. This would avoid the death of a certain group of newborns because they were associated with the most common diagnoses such as septicemia or septic shock. It is even possible to focus on the diagnosis when considering diseases in the extended TORCH group.

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