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REVIEW

WILEY PRENATAL DIAGNOSIS

Zika virus during pregnancy: From maternal exposure to congenital Zika virus syndrome

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Abstract

Zika virus (ZIKV), a vector-borne virus similar to dengue virus, was responsible for a global epidemic between 2013 and 2017 and has emerged as a new agent responsible for severe fetopathies. We present a review to describe the risks and complications of maternal and subsequent fetal infection by ZIKV. The risk of ZIKV infection during pregnancy depends on the incidence of the disease, which is highly variable in different affected geographic areas (less than 1% to 75%). Among infected pregnant women, the risk of any adverse fetal/neonatal outcome was estimated at 5% to 42%, with 1% to 4% of fetal loss and 4% to 9% of suspected congenital Zika syndrome (CZS). The estimated rate of maternal-fetal transmission ranges between 7% and 26%, depending on the methodology of the study.

Findings associated with CZS are microcephaly (33%-64%), ventriculomegaly (63%-92%), calcifications (71%-92%), malformations of cortical development (79%-82%), anomalies of the corpus callosum (71%-100%) and of the posterior fossa (21%-82%), arthrogryposis (10%-25%), eye abnormalities (25%), and extra-neurologic signs such as intra uterine growth restriction (14%), placentomegaly, transient hepatitis, mild anemia. Infants who present with CZS at birth suffer from motor abnormalities (77%-100%), epilepsy (9%-54%), hearing loss, and neurologic impairments.

Prenatal ultrasound with advanced neurosonography and appropriate virological follow-up represent the state-of-the art approach to adequately monitor at-risk pregnancies, in order to diagnose early signs of CZS and to inform parents about the neonatal prognosis.

1 | INTRODUCTION

1.1 | Characteristics and epidemiology

Zika virus (ZIKV) is a single-stranded RNA virus belonging to the *Flavivirus* genus in the *Flaviviridae* family,[1] similarly to dengue (DENV), West Nile, and yellow fever viruses. This large family is part of the arboviruses group (ie, viruses transmitted through arthropods). ZIKV was isolated for the first time in 1947 in Africa and has circulated for several decades in sub-Saharan Africa and South East Asia with only sporadic transmission to humans. Its emergence in the Pacific, in 2007, was associated with the first outbreak that occurred in Yap Islands, which was followed by the second large epidemic in French Polynesia in October 2013. From there, it spread through the Pacific and the Americas,[2,3] where it caused the massive 2015/2016 epidemic, during which the severe neurological neonatal complications

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were brought to light. ZIKV circulation declined from late 2016, but it is still circulating in late 2018, as exemplified by the first outbreaks reported in India.[4-7]

ZIKV isolates have been clustered into the ancestral African lineage and the emerging Asian lineage.[8] The strains that emerged in the Pacific and subsequently spread in the Americas are from the Asian lineage. The increase in virulence and epidemicity observed since ZIKV emerged in French Polynesia in 2013 is potentially associated with viral mutations. This does not mean, however, that strains without these mutations cannot cause severe complications.[9-11] *In vitro* and animal experiments showed that the ZIKV African lineage could infect human and mouse neuronal stem cells and is at least as efficient as the Asian strains implicated in the recent epidemics.[12-14]

Economic growth in tropical developing countries was a major driver for unprecedented and unplanned urban growth, which provided the ideal ecological conditions to increase the *Aedes* mosquito population, the mosquito vector of both ZIKV and other arboviruses such as DENV or chikungunya virus. This, combined with ineffective mosquito control and increased travel exchanges of humans and goods, provided the ideal mechanism for the emergence and spread of vector-borne transmitted diseases.[15] Moreover, previous immunity against another *Flavivirus* may be a cofactor for clinically more severe ZIKV infections through a phenomenon called Antibody Dependent Enhancement (ADE), but this has not been demonstrated.[16]

The risk of a new epidemic exists in all areas where *Aedes* competent mosquitoes are endemic and where the population is nonimmune (although it is currently unclear whether immunity is protective or might induce ADE).[17] ZIKV was first limited to enzootic circulation between nonhuman primates and sylvatic Aedes mosquitoes, before it gained the capacity to be transmitted by human adapted Aedes spp mosquitoes.[18] Since ZIKV has proven to adapt rapidly to new hosts and vectors, however, it is possible that ZIKV may emerge or reemerge in other settings than those mentioned above.

1.2 | Transmission

Like other flaviviruses, ZIKV is mainly transmitted by infected mosquitoes. The main vectors of ZIKV are *Aedes* spp. mosquitoes, principally *Aedes aegypti*, which is highly prevalent in tropical and subtropical areas, particularly in an urban setting. Other mosquitoes have proven to be competent vectors for ZIKV, in particular *Aedes albopictus*, but to date, there are no reports of ZIKV outbreaks driven by *Ae. albopictus*. Sexual transmission of ZIKV has been described, which is unique among flaviviruses.[19] Transmission of ZIKV via blood transfusion is also possible. In endemic areas, the proportion of infection due to each route of infection is, understandably, not possible to evaluate because of continuous exposure to mosquito bites.

The first reported perinatal transmission, likely occurring during delivery, was described in French Polynesia by Besnard et al.[20] Subsequently, Oliveira Melo et al isolated ZIKV in the amniotic fluid of two fetuses with significant cerebral malformations, confirming transplacental transmission.[21] The link between ZIKV and congenital abnormalities has subsequently been confirmed.[22-24] Transplacental transmission is also described for other arboviruses, but ZIKV and Venezuelan equine encephalitis virus remain the only arboviruses associated with congenital CNS malformations.[25]

ZIKV has been isolated in human milk, but milk-borne transmission has not been confirmed.[26]

What is already known about the topic?

The Zika virus (ZIKV) emergence and its consequences during pregnancy led to an increasing number of data about the maternal and fetal consequences of ZIKV infections.

What does this study add?

This review evaluates risks of maternal ZIKV infection, maternal-fetal transmission, congenital Zika syndrome (CZS), other adverse perinatal outcomes, and long-term sequelae among pregnancies exposed to ZIKV. This review also provides contemporary criteria and guidelines for the follow-up of exposed fetuses, based on prenatal and postnatal features of CZS.

2 | METHODS

A PubMed search was carried out using the terms "Zika pregnancy," "congenital Zika," and "Zika infants" and identified 1307 papers between June 2009 and November 2018. Alternative spellings were used for search terms with multiple accepted spellings (for example "CZS"). We reviewed all titles and abstracts when available and limited the search to articles reporting rates of maternal infection, maternal-fetal transmission, congenital ZIKV syndrome (CZS), adverse perinatal outcomes, and long-term sequelae among pregnancies exposed to ZIKV. We also selected papers reporting description of symptomatic maternal and congenital ZIKV infections. Guidelines providing recommendations for the diagnosis and the follow-up of ZIKV-exposed pregnancies, fetuses, and infants were also included. At least two reviewers evaluated the articles and extracted data. Searches were limited to English language. The process of article selection and the number of articles are described in a Figure S1.

3 | MATERNAL INFECTION

3.1 | Prevalence

The cumulative risk of ZIKV infection for pregnant women living in epidemic areas was reported to be 21% to 44% in cohorts from Colombia, Puerto Rico, and French Guiana,[23,27,28] but depended mainly on local incidence of ZIKV, which ranged between 1% in Brazil

after the first epidemic wave and 75% in Yap Island during the outbreak in 2007.[29,30] Risk of infection for travelers was estimated to be 1.3% during the worldwide epidemic,[31] depending on the areas visited, home conditions, and use of mosquito repellants, but has significantly dropped since the decline in circulation of ZIKV.

3.2 | Symptoms and complications

Pregnant women were symptomatic in 17% to 56% of cases of ZIKV infection.[16,23,32,33] Symptom onset may appear from the second day after infection and may last up to 2 weeks. Symptomatic infections are characterized by a maculopapular rash, mild fever, asthenia, pruritus, arthralgia, retro-orbital cephaleas, myalgia, conjunctivitis or conjunctival hyperemia, and/or edema of the extremities.[34-36] Rare severe neurological complications might occur, particularly Guillain-Barré syndrome, which may be a life-threatening condition in pregnant women (prevalence of 1.23% (95% CI, 1.17%-1.29%) in general infected-population).[37,38] However, pregnancy is not associated with more frequent or more severe maternal complications.[32] The presence and the severity of maternal symptoms are not associated with a higher risk of birth defects or fetal loss.[39,40] Although a persistent viremia was initially associated with a higher risk of birth defects, no recent studies have been able to determine if viral load or prolonged viremia represented risk factors for adverse fetal or neonatal outcomes.[23,40,41]

3.3 | Diagnosis

Since most ZIKV-infected pregnant women are asymptomatic and symptoms are nonspecific,[32] a biological confirmation of the infection is required. According to the United States Centers for Disease Control and Prevention (CDC) guidelines, ZIKV testing is currently recommended for every symptomatic pregnant women with possible ZIKV exposure, for asymptomatic pregnant women with ongoing possible ZIKV exposure and for ZIKV-exposed pregnant women whose fetus presents with prenatal US findings consistent with congenital ZIKV infection. ZIKV testing may also be considered for asymptomatic pregnant women with recent possible but not ongoing exposure to ZIKV (ie, travelers)[42] (https://www.cdc.gov/pregnancy/zika/testing-follow-up/documents/testing-algorithm-asymptomatic.pdf).[43] However, since birth defects were described in asymptomatic ZIKV-infected pregnant women returning from endemic areas,[44] ZIKV testing should be offered to all pregnant women possibly exposed to ZIKV. If symptoms compatible with ZIKV infection are identified, nucleic acid test (NAT) or ZIKV RNA amplification by reverse transcription polymerase chain reaction (RT-PCR) should be performed in serum/blood and urine as soon as possible and up to 12 weeks after symptom onset, according to CDC guidelines. ZIKV can be detected in blood most often within the first weeks after symptoms onset. In urine, the window of detection is increased up to 2 to 3 weeks after infection. A positive NAT or RT-PCR in any body fluid confirms the diagnosis. Nevertheless, as false positive results have been described, the CDC recommends positive NAT, to be confirmed by a second set of testing, an approach that may not always be possible during an active epidemic, because of limited laboratory capabilities. A negative result does not exclude ZIKV infection, because of the transient presence of the virus in infected patients. CDC recommends to perform NAT three times during pregnancy for asymptomatic pregnant women with ongoing exposure to ZIKV. However, because of differences in serological and virological assays available, particularly in developing and low-income countries, testing guidelines may differ from country to country, and ZIKV serology may also be considered for women living in an area of active ZIKV transmission.[43]

Serologic evaluation for ZIKV infection includes an initial screening by enzyme-linked immunosorbent assay (ELISA) to detect specific class M immunoglobulins (IgM) against ZIKV followed by confirmation testing by plaque reduction neutralization test (PRNT) due to cross-reactivity with other flaviviruses.[45] Indirect immunofluorescence and ELISA are both adequate approaches for detecting ZIKV-IgG, but must be considered jointly with other laboratory results, particularly PRNT, due to low specificity of IgG. The sensitivity and negative predictive value of the serological results are controversial, since some patients remain serologically negative despite proven infection (RNA amplification), and false positive results due to cross reaction are possible even using PRNT.[46] For women with ongoing exposure, serological assays are not appropriate to the determination of timing of the acute infection in relation to the beginning of the pregnancy. Nevertheless, serological diagnosis based on IgM remains a reliable tool, particularly in women without co/previous exposure to arboviruses.

A recent update in the World Health Organization (WHO) classification for ZIKV cases defines a suspected case as a person presenting with a rash and/or fever and at least one of arthralgia, arthritis, or conjunctivitis. Probable cases are defined as presence of specific IgM antibodies against ZIKV with an epidemiological link. Confirmed cases are defined as detection of ZIKV RNA or antigen in any body fluid or presence of IgM antibodies against ZIKV plus PRNT for ZIKV with a titer greater than or equal to 20 and titer ratio greater than or equal to 4 compared with other flaviviruses.[47]

4 | CONGENITAL ZIKV SYNDROME

4.1 | Definition of Congenital ZIKV syndrome

Although still controversial, the CDC defines CZS as a proven *in utero* ZIKV infection associated with severe microcephaly in which the skull has partially collapsed, decreased brain tissue with a specific pattern of brain damage (including subcortical calcifications), damage to the back of the eye (including macular scarring and focal pigmentary retinal mottling), congenital contractures (clubfoot or arthrogryposis), hypertonia, or restricted body movement soon after birth.[48]

A more restrictive definition of CZS was published by Moore et al, based on advanced clinical and neurological features, postnatal imaging (magnetic resonance imaging [MRI]), and fundoscopy.[49]

In the cohort from French Guiana, we proposed a definition based on early neonatal clinical, biological, and imaging features,

differentiating neonates with signs potentially associated with CZS and those with complications compatible with CZS.[50]

In future epidemics, other more subtle signs might be associated with CZS, and some infected infants may only develop anomalies in childhood.[51,52]

Semiology and characteristics of CZS are described in Table 1.

4.2 | Prenatal features of CZS

Although the first reports showed an association between microcephaly and ZIKV materno-fetal infection,[21,53] many case series and cohorts have shown that microcephaly is not consistently present in CZS, and that ultrasound (US) examination must pay particular attention to the brain anatomy.[23,24,54,55]

4.2.1 | Microcephaly

Most current guidelines define microcephaly as a head circumference (HC) below the third percentile (less than 2 standard deviations [SD]), and the term "severe microcephaly" is used for a HC of less than 3 SD on reference charts (Intergrowth 21st references can be used[56]). For different reasons, however, caution is required on prenatal US, since HC measurements are not always accurate, most fetuses with an HC between −2 and −3 SD will develop normally, and the estimation of brain growth may be distorted by a normal head size with large peri-

TABLE 1 Characteristics of congenital Zika virus syndrome

		Major Signs	Minor Signs
Prenatal and postnatal imaging/Birth defects (Ultrasonography, MRI, CT-scan, and autopsy)	Cerebral	Fetal brain disruption sequence[a]	
		Severe microcephaly < −3 SD	Mild microcephaly < −2 SD
		Ventriculomegaly >12 mm	Mild ventriculomegaly >10 mm
		Cisterna magna >10 mm	subependymal cysts
		Multiple linear or punctiform calcifications	Isolated intracerebral calcification
		Dys/agenesis of corpus callosum	Hypoplasia of corpus callosum
		Vermian dysgenesis	Vermian hypoplasia
		Brainstem dysgenesis	Lenticulostriate vessels vasculopathy
		Porencehaply	Choroid plexus cysts
		Periventricular cystic lesions	Irregular periventricular halo
		MCD[b]	Intraventricular adhesions
	Extra-cerebral	Fetal hydrops	Oligo/polyhydramnios
		Arthrogryposis	IUGR
		Ocular anomalies	Hyperechogenic bowel
			Ascite, subcutaneous edema
			Placentomegaly >40 mm
			Hepato/splenomegaly
Clinical signs		Hypertonia	Hypotonia
		Swallowing disorder	SGA
		HC < −3 SD	HC < −2 SD
		Arthrogryposis	Partial immobilism
		Epilepsy	Hepato/splenomegaly
			Jaundice
			Tremors and extrapyramidal symptoms
			Cognitive disabilities
			Hearing impairment
			Hyperexcitability, impatient crying
			Sleeping disorders
Ocular anomalies		Microphtalmia	Cataract
		Coloboma	Posterior anomalies
			Chorioretinal atrophy
			Focal pigmentary mottling
			Optic nerve hypoplasia/atrophy
Biological parameters			Hb < 140 g/L
			AST > 100 U/L
			ALT > 100 U/L

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; HC; head circumference; IUGR, intra-uterine growth restriction; SD, standard deviation; SGA, small for gestational age; Tc, Thrombocytes. Adapted from Pomar et al.[50]

[a]Fetal brain dysruption sequence: Severe microcephaly, premature closure of fontanels, collapsed skull, overlapping sutures, redundant scalp skin

[b]Malformations of cortical development (MCD): lissencephaly, agyria, pachygyria, polymicrogyria, and heterotopia

cerebral spaces, masking a "micro-encephaly." Microcephaly related to CZS is generally associated with an atypical skull shape and an occipital excess of skin, suggesting a fetal brain disruption sequence. In our and others experience, microcephaly is always associated with other findings and seems to be the consequence of viral brain injury. Prevalence of microcephaly in CZS is 33.3% to 64 %, but brain volume loss seems to be much more frequent (92% of cases).[57-59]

4.2.2 | Ventriculomegaly

Ventriculomegaly induced by ZIKV is often asymmetrical or unilateral, suggesting focal injury more than a compression model found in other infections (stenosis of the Sylvius aqueduct and obstruction by a necrotic process).[57] Ventriculomegaly associated with ZIKV is probably related to the atrophic brain, peri-ventricular, and germinative necrosis, as suggested by the thin cortical mantle frequently observed. Prevalence of ventriculomegaly in CZS is 63.1% to 92%.[57-59]

4.2.3 | Calcifications

Calcifications caused by focal necrosis are common in CZS. These calcifications are often weakly echogenic without any posterior shadowing on prenatal US[60-63] and can intensify in echogenicity and size during pregnancy, which may lead to multiple punctiform macrocalcifications.[57,60] Prevalence of calcifications in CZS is 71% to 92%.[57,58]

The calcifications can be localized to any part of the brain with particular predilection for the cortical-subcortical junction and the periventricular zone; calcifications have also been identified in the midbrain, nucleus caudate, brainstem, cerebellum, basal ganglia, and spinal cord as described in other TORCH (toxoplasmosis, others, rubella, cytomegalovirus, herpes virus) infections.[57,64]

4.2.4 | Malformations of cortical development

Abnormal neuronal migration and disorders of cortical development are visualized by reduction in gyration (pachy/agyria), polymicrogyria, heterotopias, and subsequent microcephaly.[57,65] Malformations of cortical development were described in 79% to 82% of CZS cases.[57,58]

In addition, destructive cystic diseases such as porencephaly, schizencephaly, or hydranencephaly are frequently observed because of necrosis of neural progenitors. Similar destructive lesions are frequently observed in other congenital infections.[66-68] Ventricular hemorrhages, which reflect bleeding in the highly vascularized germinal matrix have not been associated with CZS, whereas lesions of the germinal matrix, including subependymal pseudocysts,[60] have been observed in several reports.[23,69] Subependymal pseudocysts are thought to precede germinal matrix hemorrhages and are frequently observed in premature newborns.[70] Although most of these pseudocysts are benign, they can be associated with dismal prognosis due to early destruction of the germinal matrix when they are located in the occipital or temporal horn.[71] Intraventricular synechiae and periventricular cystic degeneration may also develop, as in congenital cytomegalovirus (CMV), and was reported in 58% of CZS cases in the Colombian cohort.[57,72]

4.2.5 | Corpus callosum dysgenesis

Dysgenesis of the corpus callosum is frequently described including partial or complete agenesis and callosal calcifications.[57,64,69] Prevalence of malformations of the corpus callosum range between 71% and 100%.[57,58]

4.2.6 | Posterior fossa anomalies

Mega cisterna magna is also described, which may represent a Dandy-Walker malformation or vermian hypoplasia/dysgenesis, especially when an enlarged cisterna magna is found early in pregnancy.[23,57,65] Vermian hypoplasia and global cerebellar hypoplasia were reported in 42% and 21% to 82% of CZS cases, respectively.[57,73] The brainstem can also be hypoplastic or dysplastic and is associated with extra-cerebral abnormalities such as swallowing disorders and hydramnios (25%) as well as partial immobilization or arthrogryposes (10%-25%).[57,60,64,74,75]

4.2.7 | Eye abnormalities

The eye disorders observed on prenatal US or MRI can range from the more common unilateral microphthalmia to anophthalmia.[21,23,57] The spectrum of optical abnormalities found postnatally is larger, including signs that can be found in prenatal imaging: optic chiasm hypoplasia, coloboma of the retina, and cataract.[23,76] Prevalence of eye abnormalities in CZS is approximately 25%.[57,77]

4.2.8 | Extra-cerebral anomalies

Signs of placental inflammation such as increased thickness (placentomegaly) and calcifications have been observed in some cases.[61,78] Placental dysfunction induced by ZIKV infection may contribute to the development of fetal damage or intrauterine growth restriction (IUGR), particularly in cases of early infection when placental circulation is not yet established.[79] Overall, IUGR was observed in 14% of CZS cases and could be the result of both fetal infection and placental insufficiency.[34,79]

4.3 | Clinical features of CZS at birth

Mild anemia, cholestasis, and transient hepatitis have been found in fetuses and newborns infected by ZIKV.[80,81]

Neurologic impairments such as swallowing dysfunction, movement abnormalities, and epilepsy have been described in infants suffering from CZS as well as in infants asymptomatic at birth.[82]

The predominant neurologic findings in young infants with suspected congenital ZIKV infection are extreme irritability, hyperreflexia, and hypertonia with spasticity, tremors, and extrapyramidal symptoms, hypotonia, or a combination of hyper- and

hypotonia.[36,63,83,84] Motor abnormalities affected 77.3% to 100% of infants with CZS at birth.[82,85] Epilepsy is associated with 9% to 95.5% of congenital ZIKV infection.[59,82-87]

Another study reported feeding challenges, sleeping difficulties, severe motor impairment, vision and hearing abnormalities, and/or seizures disorders in all 18- to 24-month old infants born with CZS.[88] Long-term sequelae, particularly regarding neuro-development and cognitive function of these infants, however, remain insufficiently investigated.[75]

5 | MANAGEMENT OF EXPOSED PREGNANCIES AND RECOMMANDATIONS

5.1 | Maternal-fetal transmission of ZIKV

In a cohort evaluated in French Guiana, we first estimated the maternal-fetal transmission rate at 10.9%, based on amniocentesis and serology results of the newborns.[23] After extensive investigation on fetal/neonatal (amniotic fluid, fetal and neonatal blood, cerebrospinal fluid, urine) and placental samples of 291 fetuses/newborns, the vertical transmission rate was estimated at 26.1%. When positive placenta samples were removed from the analysis because of the theoretical risk of placental contamination by maternal viremia, the vertical transmission rate was estimated at 18%.[50] The New-York City cohort of ZIKV-exposed pregnant women reported proof of a congenital infection in 7% of confirmed or probable maternal ZIKV infections.[89] Available data do not seem to indicate an increased rate of maternal-fetal transmission with ongoing gestation, as for example in congenital toxoplasmosis. However, more studies are required to conclude on the evolution of transplacental infection according to the timing of maternal infection.

Overall, maternal-fetal transmission of ZIKV remains difficult to estimate because of the debatable sensitivity and specificity of ELISA, that ZIKV RNA is only transiently present in blood, urine, and amniotic fluid[81] and depends on the fetal samples investigated.[50]

5.2 | Prevalence of adverse outcomes

At the beginning of the ZIKV epidemic, first reports announced fetal abnormalities linked to maternal ZIKV infection in more than 40% of cases.[36] These reports included "any abnormalities," such as an isolated Doppler anomaly or "small HC < −1 SD" and led to a global overestimation of the consequences of ZIKV infections during pregnancy.

Recent reports, with more extensive investigations of fetuses and newborns, reported CZS in 4% to 9% of pregnancies exposed to ZIKV, when exposure is defined by proven maternal infection.[23,33,35,57,61,87]

In a recent study investigating the rate of adverse outcomes in proven infected fetuses/newborns, 45% presented with no signs/complications, 20% had mild/moderate signs potentially correlated to congenital Zika virus infection (cZIKV) infection, 21% had severe complications compatible with CZS, and 14% resulted in fetal loss.[50]

Maternal infection during the first trimester of pregnancy is associated with a higher risk of miscarriage, fetal loss or CZS; whereas an infection in late pregnancy seems to have less fetal and early neonatal consequences, with unspecific signs, as for others TORCH infections.[23,35,60,90,91]

A recent report of the US Zika Pregnancy and Infant Registry noted a risk of neurodevelopmental abnormality in 9% of infants (1 year of age) born from infected mothers.[87] Overall, the risk of postnatal neurological sequelae in congenitally infected infants without prenatal findings indicative of CZS remains unknown. Ongoing investigation of several cohorts might increase the knowledge on later sequelae associated with congenital ZIKV infection.

Risks associated with maternal and fetal ZIKV infection are described in Figure 1.

5.3 | Follow-up of exposed pregnant women

An enhanced US follow-up schedule for all exposed pregnant women regardless of their status, with detailed fetal neurosonography for those who presented with positive laboratory testing, aims to increase the sensitivity of the detection of CZS. The "International Society of Ultrasound in Obstetrics and Gynecology" (ISUOG) and several national organizations recommend detailed US examination on a monthly basis.[23,92,93] When ZIKV maternal infection is suspected or confirmed, neurosonographic examinations of the fetus should be performed in a referral center, as is done for other congenital infections during pregnancy.

When time of infection is known, a delay[23,57,63] of 3 to 15 weeks[63] was observed before identification of early fetal abnormalities.

In addition to US, MRI represents a complementary tool when neurosonography is limited or not available to evaluate congenital ZIKV infections, particulary after 30 weeks gestation, to facilitate an appropriate examination of the gyration and to highlight increased cerebro-spinal fluid, migration disorders, or cortical development anomalies.[21,57,73]

Recommendations for prenatal and postnatal follow-up of exposed fetuses are available in Figure 2.

5.4 | Prenatal diagnosis and management of CZS

The prenatal diagnosis of CZS depends on the attribution of the observed lesions to ZIKV.

When fetal status is unknown in an infected mother, any US abnormality can predict a CZS in only 41.3% of cases in an epidemic area.[94] Even if a severe CNS malformation is present, other etiologies must be disproved.[95]

If one or more of the abnormalities described above are encountered, an amniocentesis should be proposed in order to perform ZIKV RT-PCR, other TORCH PCRs and karyotype (and/or CGH array) to confirm the diagnosis of CZS and to exclude other possible causes.

By analogy to other congenital infections, the virus is probably only shed in the amniotic fluid once a sufficient time has elapsed for the

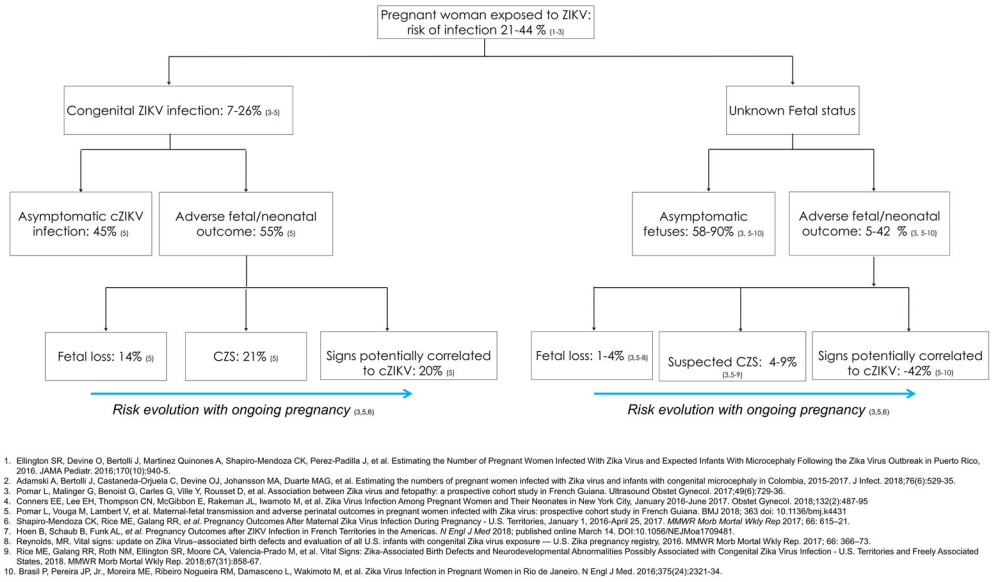

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FIGURE 1 Risks of maternal infection, fetal infection and adverse outcomes. Abbreviations: cZIKV, congenital zika virus infection; CZS, congenital zika virus syndrome; ZIKV, zika virus (Adapted from Pomar et al[50]) [Colour figure can be viewed at wileyonlinelibrary.com]

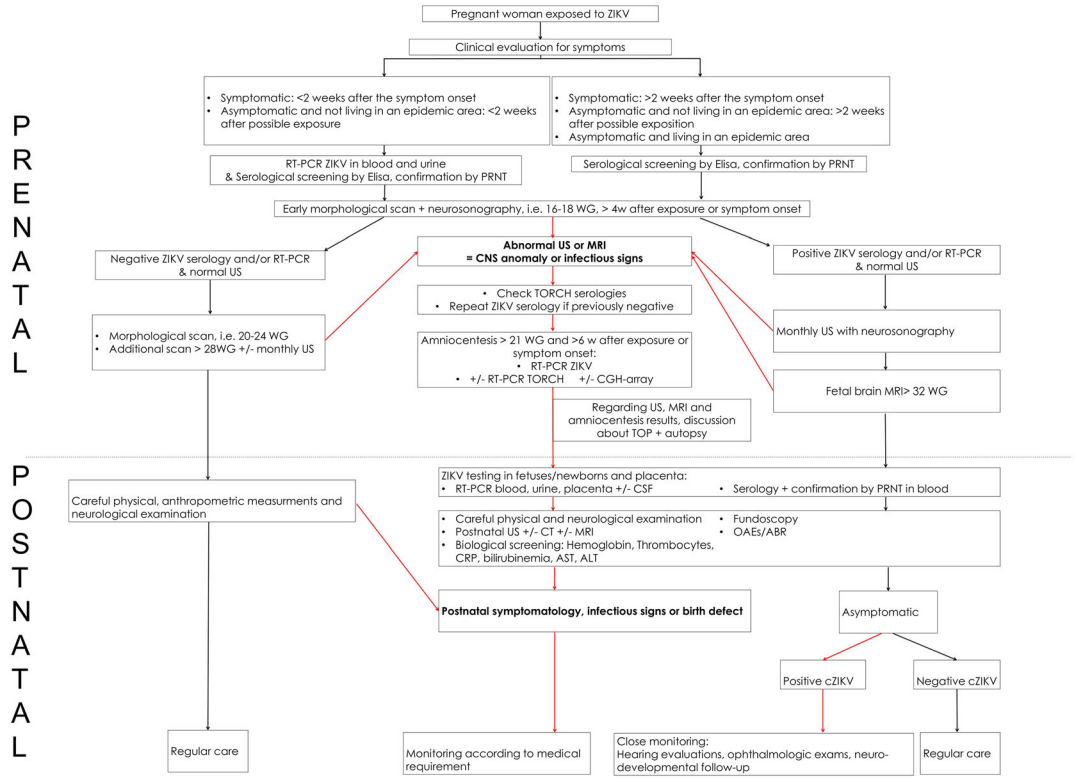

FIGURE 2 Clinical follow-up of exposed pregnant women, fetuses, and newborns. Abbreviations: ABR, auditory brainstem response; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebro-spinal fluid; cZIKV, congenital zika virus infection; MRI, magnetic resonance imaging; OAE, oto-acoustic emission; PRNT, plaque reduction neutralization test; RT-PCR, reverse transcriptase polymerase chain reaction; TOP, termination of pregnancy; US, ultrasound; WG, weeks' gestation; ZIKV, Zika virus (Adapted from Vouga et al[97]) [Colour figure can be viewed at wileyonlinelibrary.com]

virus to breach the placental barrier (6-8 weeks after infection) and once the fetal kidneys produce sufficient urine.[96,97] The sensitivity of amniocentesis remains unknown because of the lack of knowledge about the evolution of viremia. Schaub et al showed that ZIKV RNA amplification could be transient in the amniotic fluid, fetal blood, and placenta.[81] Thus, ZIKV may no longer be detectable after a prolonged

time from the initial infection, since ZIKV secretion by the fetal kidney is probably transient, and RNA is less stable than DNA (ie, CMV). Current recommendations, based on these highlights, suggest that amniocentesis should be offered only in the presence of fetal signs, 6 to 8 weeks after suspected maternal exposure and after 21 weeks' gestation,[97] taking into account that a negative result does not rule out ZIKV congenital infection. Also, a positive ZIKV result does not exclude other fetal chromosomal or infectious pathologies.[95]

Schaub et al described the biological responses to ZIKV infection in fetal blood, such as transient anemia or increased liver enzyme levels.[81] It is yet unknown whether these markers of infection or viral loads in fetal blood are prognostic factors, such as in congenital CMV infection.[98]

Unrelated to the serological findings, the presence of a CNS malformation related to intrauterine infection is associated with a poor prognosis in more than 90% of cases, and in these cases, termination of pregnancy should be considered in accordance with the country's laws.

5.5 | Postnatal diagnosis of CZS and follow-up

The confirmation of an *in-utero* infection can be made from a positive RT-PCR on cord blood, neonatal blood, urine, placenta, or cerebrospinal fluid, as well as the presence of specific IgM.

Positive cord blood should be confirmed on neonatal blood in order to exclude potential maternal contamination.

Postnatal recommendations include clinical, biological, and imaging follow-up, adapted to the ZIKV-status of the newborn and to the presence of signs or symptoms (described in Figure 2).

6 | TREATMENT AND PREVENTION

6.1 | Prevention

Pregnant women and couples planning to start a pregnancy should avoid travel in epidemic areas. When there is a need to travel to or for those living in endemic areas, avoiding mosquito bites using long clothing and repellant is proposed.

Because of the prolonged persistence of ZIKV RNA in semen, the first recommendations issued by the European Centers for Disease Control and Prevention, the WHO, and different health ministries suggested postponement of any pregnancy attempts for at least 6 months for men and 2 months for women after the last possible exposure to the virus.[47] Because of the decline of ZIKV and exceptional persistence of infective viral particles in semen,[99] this delay has been reduced to 3 months for men and remains 2 months for women.[100]

6.2 | Potential therapeutic options

To our knowledge, there is currently no drug licensed against any arboviruses. We review the ongoing research and clinical trials for Zika below.

6.2.1 | Vaccines

Promising DNA, mRNA, and purified inactivated virus vaccines that could be used to prevent ZIKV are currently in phase I[101] or phase II clinical trials.[102,103]

6.2.2 | Antiretroviral

To limit the development of CZS, two strategies might be evaluated: to treat the infected mother in order to reduce maternal viral replication and subsequent transplacental transmission and to focus on the reduction of symptoms in infected fetuses, as it has been tried in cCMV infections with Valacyclovir.[104] Recent *in vitro* and *in vivo* models show good efficacy of Sobosbuvir to reduce the viral burden and vertical transmission in animals.[105]

7 | CONCLUSION

This review presents an estimation of the risk of infection by ZIKV for pregnant women and their fetus/newborn and subsequent risks of complications. Prenatal US with advanced neurosonography and appropriate virological follow-up represent a gold standard to adequately monitor at-risk pregnancies, in order to diagnose early signs of CZS and to inform parents about the neonatal prognosis. Long-term sequelae are still not well described, and long-term cohorts are needed to accurately define the burden of ZIKV in childhood.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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