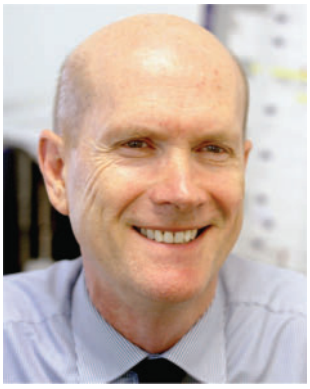
Arboviruses in pregnancy: consequences of maternal and fetal infection



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Epidemics and localised outbreaks of infections due to arthropod borne (arbo) viruses, have been described for hundreds of years. Few viruses to date are known to transmit from mother to fetus, causing either teratogenic effects or fetal demise (see recent reviews Charlier *et al.*[1] and Marinho *et al.*[2]). Many arboviruses are zoonotic but there appear to be few parallels between the effect of these viruses following human or animal infection during pregnancy. Higher rates of MTCT (mother to child transmission) may be seen (1) where herd immunity is reduced, either because virus is newly introduced into a population (as occurred in Brazil with ZIKV), or where the virus has only recently become endemic (as occurred with West Nile virus (WNV) in the USA in the 1990s), (2) where the arthropod vector is present, (3) where the vector transmits virus efficiently, and (4) in groups of pregnant women exposed, allowing transmission[3].

Transmission

There are ~200 million pregnancies annually worldwide, with 90% in regions where arboviruses are endemic: often these are regions with reduced diagnostic capacity[4]. Arbovirus epidemics have the potential for significant outbreaks of disease in pregnant women and their unborn infants, as evidenced by ZIKV in Brazil where ~17 000 pregnant women had been infected by April 2017[5]. Except for DENV and ZIKV, much is unknown about MTCT of arboviruses, the antenatal and perinatal effects of infection are not well described, and mechanisms of viral teratogenicity are only recognised for some arboviruses[1]. This means links between adverse pregnancy outcomes and arboviral infections are problematic, particularly where the clinical outcomes are mild, develop over time or are subtle, such as failure to thrive, and mild neurodevelopmental delay.

Effects on the mother

Pregnant women suffer similar symptoms and signs as non-pregnant women, although in general terms, they have a higher risk of more severe effects of viral infection due to the immunosuppression of pregnancy[6]. The typical syndromes include short incubation time (<1 week), fever, malaise, rash, encephalitis/meningoencephalitis, or haemorrhagic fever (Table 1). Maternal and other infections are asymptomatic in 70–80% of infected individuals, excepting CHIKV (>95% symptomatic often with severe arthritis)[8], Yellow fever virus (YFV, ~50% symptomatic)[9], and ZIKV Asian lineage (~50% symptomatic with prominent pruritic rash and arthritis)[10]. Infection in pregnancy with DENV results in increased maternal mortality and severe illness (OR 3.38, 95% CI 2.1–5.42), increased caesarean section and increased postpartum haemorrhages[11].

Effects on the fetus and newborn

It remains uncertain whether arboviral infection causes fetal damage through direct fetal infection when it occurs, and/or as a result of placental dysfunction causing fetal damage through malnutrition and reduced function, as occurs in other congenital infections[12,13]. The fetal and neonatal disease caused by arbovirus infection includes fetal demise, premature birth, and neurodevelopmental defects from viral teratogenicity. The latter has been recognised particularly with ZIKV and Venezuelan equine encephalitis (VEE) virus infections, as summarised in Table 1, and in recent reviews[1,2]. Ross River Virus infection may cause fetal infection, although it is uncertain if fetal disease results[14–16].

DENV is the most common arboviral infection globally, and is associated with severe illness *in utero*, including premature birth (21% versus background rate 11.5%), and miscarriage particularly during the first trimester (T1), and fetal death (13% versus background *in utero* death rate of 1.8%)[11]. Maternal symptomatic presentation correlates with rates of fetal demise, with no clear association with serotype. The immune enhancement syndrome seen with second infection from a serotype discordant with a prior DENV serotype infection is also seen in pregnant women, and the fetus[17]. Other arboviruses appear to less frequently affect the fetus[18,19].

Table 1. Some arboviruses of significance in pregnancy.

Virus	Virus family	Distribution	Clinical presentation acute disease	Major fetal effects
Chikungunya (CHIKV)	Alpha (Toga)	• 1952 Initially Tanzania • 1958 Asia • 2013 Americas • 2014 Brazil	IP 2–10 days (1–12 days) Duration 7–10 days • Fever • Arthralgia • Rash	VT 27–48% • Newborn fever, irritability • Postnatal global neurodevelopmental delay • Fetal demise • TG
Dengue (DENV types 1, 2, 3, 4)	Flavi	• DENV – like for centuries • 1943 isolated Japan (DENV1) • 1945 Hawaii (DENV2)	IP 3–10 days • Fever • Rash • Myalgia • 3 phases • 2015 Live attenuated vaccine	VT • MC • Fetal demise • Prematurity • TG not reported
Japanese Encephalitis (JEV)	Flavi	• Asia for centuries	IP 5–15 days • Fever • Myalgia • Headache • Vaccine	VT rare • Fetal demise • Neurological infection
West Nile Virus (WNV)	Flavi	• Africa • Asia • Middle East • 1999 USA • 2000 Mediterranean France	IP 3–14 days • Asymptomatic 80% • Meningoencephalitis	VT rare • TG with brain malformation • Retinal scarring, neurological disease • Miscarriage T1 • T3 transmission with perinatal neurological disease
Yellow fever (YFV)	Flavi	• Africa for centuries • 1700s Americas • 2015 Angola urban • 2017 Brazil	IP 3–6 days • Fever • Myalgia • Headache • 1930 live attenuated vaccine	PT • Newborn fever, hepatitis, death
Zika (ZIKV)	Flavi African Asian lineages	• 1947 Initially Uganda • 1954 Nigeria • 1969 Outside Africa • 2007 Micronesia (Yap) • 2015 Brazil	IP 4–5 days 80% asymptomatic Clinically as for non-pregnant • Rash • Fever • Arthralgia, myalgia • Conjunctivitis	VT Fetal disease worst T1 • Neurological syndromes • Microcephaly • Fetal demise

VT, vertical transmission; MC, miscarriage; PT, perinatal transmission; IP, incubation period range from systematic review Rudolph *et al.*[7]; TG, teratogenicity; T, trimester of pregnancy.

The most prominent recent arbovirus-induced fetal malformation has been ZIKV infection, particularly with the Asian lineage in the Americas. This outbreak, initially most severe in Brazil, has been discussed in this journal[20], and elsewhere by those at the forefront of epidemic response[21–23], and more recently in the United States of America[24]. It has become clear that regarding ZIKV: (1) infection in pregnant women may result in fetal demise, intrauterine growth restriction, microcephaly, and neurological abnormalities[25]; (2) disease includes abnormalities of the eye, hearing, craniofacial area, musculoskeletal system; (3) a range of pathological changes occur, with brain abnormalities present in 1–13% of infants of mothers with ZIKV infection; (4) the highest, but not only, risk period is T1, T2; (5) apparently healthy neonates born following maternal ZIKV infection may have longterm neurodevelopmental adverse outcomes; (6) not all outbreaks produce identical phenotypes of fetal and neonatal disease, although infections during pregnancy predominantly result in neurological adverse outcomes of varying severity, (7) screening for ZIKV in pregnant women has

been recommended for at-risk populations[5]; and (8) ZIKV is spread sexually, unusually for an arthropod borne virus, and such spread may result from seminal ZIKV present for up to 120 days in semen, albeit at low titre[26].

The diagnosis of arbovirus infections in pregnancy utilises standard molecular methods (predominantly arbovirus specific RT-PCR of blood, cerebrospinal fluid, urine, saliva) and serology (predominantly EIA for detecting virus-specific IgG, IgM), with evidence of seroconversion where specimens are available. There are a range of commercial diagnostic assays available but they vary significantly in their sensitivity and specificity and require care when interpreting results[27].

Control of arbovirus infections

Many editorials discuss that recent ZIKV outbreaks highlight the effects of arboviruses on pregnant women, rather than ZIKV being the only cause of virus-induced congenital malformation[28]. Of the arboviruses known to pose a risk to pregnancy (Table 1), there are vaccines against YFV, JEV and WNV, with vaccines against DENV, CHIKV and ZIKV in various stages of development and testing. Sexual transmission of these viruses (particularly ZIKV) including from asymptomatic hosts, poses a significant challenge. Guidelines are available to inform efforts to minimise this risk. As public health and vaccine efforts are enhanced, it is hoped control of MTCT and neonatal disease from arboviruses will improve.

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Biography

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