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Materno-foetal arbovirus transmission

Arboviruses are known to undergo materno-foetal transmission. Such transmission has been described for dengue fever, Japanese encephalitis, and infections with West Nile virus, chikungunya and Zika virus. The pathogenesis can only become more widespread, given the global rise in arbovirus transmission by mosquitoes. Some arboviruses belonging to the genera *Flavivirus* and *Alphavirus* are able to cross the placental barrier in a small number of pregnant women.

Aedes aegypti in the Caribbean and _Aedes albopictus_ in metropolitan France and Réunion are the vectors of dengue fever and chikungunya. Materno-foetal transmission of arboviruses can occur at any stage of pregnancy: they are generally rare but severe during the early stages of pregnancy, and more frequent but less severe towards the end of pregnancy. There is a high risk of transmission to the newborn during delivery if the mother is in a period of viraemia.

Dengue Fever

All four dengue flaviviruses (DEN 1, DEN 2, DEN 3, and DEN 4) may disrupt the pregnancy and threaten the life of the unborn child.

In pregnant women, the clinical symptoms are no different to those normally associated with dengue fever (sudden high fever for 2 to 7 days, with diffuse pain, rash, and petechiae).

During pregnancy and until a few days before delivery, maternal dengue fever has the standard characteristics of dengue fever (sudden high fever, with pain and signs of haemorrhage), but there is additional exacerbation of the complications of pregnancy: thrombocytopenia, haemolysis, and elevated liver enzymes.

The obstetric consequences are primarily as follows:

- Elevated rate of spontaneous miscarriage during the 1st trimester, and a higher rate of in utero foetal death (13% vs. 1.8% in the general population)
- There are no reports of teratogenic effects
- Higher rate of premature birth (21% vs. 11.5% in the general population)
- Elevated risk of acute uterine bleeding during delivery

Congenital dengue fever is caused by the transplacental transmission of the virus in the days before delivery (direct transmission of the virus to the child). Congenital dengue fever is reported in endemic areas. In the newborn, the first signs appear between Day 1 and Day 11, and last for between 1 and 5 days. In infants, the signs are highly variable, ranging from asymptomatic forms to the usual manifestations of dengue fever: high fever, sometimes associated with thrombocytopenia, or severe cases with respiratory distress or haemodynamic failure, potentially leading to the death of the newborn.

Maternal antibodies cross the placental barrier and protect the child during the first six months of life.

To date, individual protection against mosquitoes is the only effective means of prevention.

In December 2015, marketing authorisation was granted for a vaccine (Dengvaxia®). This vaccine is effective against the four serotypes of dengue, but its use is restricted to endemic areas. It is a live attenuated vaccine and is therefore contraindicated during pregnancy.

Chikungunya

The alphavirus responsible for chikungunya is also transmitted by Aedes mosquito bites. Bites occur outside during the day, especially at dusk and dawn.

This virus can be transmitted from mother to foetus during pregnancy. Materno-foetal transmission is very rare before Week 22 of pregnancy and can be detected by RT-PCR analysis of amniotic fluid. During this period, the prognosis is poor and

associated with a high risk of in utero foetal death. After Week 22 of pregnancy, the risk to the foetus is low to non-existent.

Most materno-foetal transmission occurs during the peripartum period, from 2 days before to 2 days after delivery, with viraemic mothers. In these cases, the rate of materno-foetal transmission is 50%. In some cases the mother remains asymptomatic, and the diagnosis is therefore retrospective. However, most cases present with fever and diffuse pain, particularly joint pain, accompanied by rash.

Neonates are asymptomatic at birth then develop rash with erythroderma 3 to 7 days after the mother, followed by fever and pain, then gastrointestinal signs (refusal to breastfeed, diarrhoea), and finally severe oedema followed by desquamation of the extremities. There may be neurological complications (seizures, abnormal neurological examination and EEG results). Coagulation disorders (DIC) and intracerebral haemorrhage may also occur.

The main preventive measures are vector control (elimination of natural and artificial sources of stagnant water) and individual protection against mosquitoes.

West Nile virus

This is an arbovirus of the genus *Flavivirus*, transmitted by the female *Culex* mosquito. The natural reservoir is wild and migratory birds, and horses and humans are accidental hosts.

This disease is epidemic in Asia, Africa, the Middle East, and central Europe, and also in the USA and the Mediterranean regions of France since the 2000s.

Clinically, 80% of cases are asymptomatic, whereas the remaining patients develop sudden high fever with headache, pain, swelling of the cervical lymph nodes, and meningoencephalitis-type neurological complications in 1% of cases.

Materno-foetal transmission and congenital infection are possible but very rare; they are associated with malformations, particularly of the brain. During the first trimester of pregnancy, infection is associated with a higher risk of spontaneous abortions. Nonetheless, there are reported cases of mothers who developed meningoencephalitis from West Nile virus infection during early pregnancy and gave birth to healthy babies. Materno-foetal transmission during the last month of pregnancy with severe neurological complications in the newborn has also been described.

The low risk of transmission is probably due to the low maternal viraemia.

Prevention also relies on vector control and individual protection against mosquitoes.

Japanese encephalitis

This type of *Flavivirus* infection has a very broad geographic range in Asia, and severe neurological manifestations are reported for 1 in every 25–1000 infected subjects. It is the primary cause of encephalitis in Asia. Cases of materno-foetal transmission are rare.

There is a major risk of foetal death during the first half of pregnancy. Mothers infected during the second half of pregnancy have given birth to apparently healthy babies.

A vaccine is currently available in several Asian countries.

Zika virus

Zika virus is a *Flavivirus* transmitted by the bite of the Aedes mosquito. The virus is named after the Zika forest in Uganda where it was first discovered in a rhesus monkey in 1947. The virus was later isolated in humans with fever in West Africa. After spreading at global level, it is now regularly encountered in Africa and Asia. There are two Zika virus lineages: an African lineage and an Asian lineage. These are responsible for epidemics in many countries: Indonesia, Micronesia, Thailand, Philippines. Since late 2015, an epidemic has spread across South America, Central America and the Caribbean region (Asian lineage).

Vector-borne transmission is the most common, through bites of the female mosquito, but transmission by blood transfusion is also possible if the blood was collected from a donor in the viraemic phase. Viraemia is short-lived at between 2 and 7 days.

Sexual transmission has been demonstrated; and the virus has been detected in semen by PCR. The duration of positive virus detection in sperm in a patient who has been in contact with Zika has not yet been determined, but there are reported cases of positive sperm findings 90 days after suspected contact with the infectious agent.

The clinical presentation in pregnant women does not differ from that in other patients: in 70 to 80% of cases the infection is asymptomatic; in other cases, a maculopapular rash, sometimes pruritic, can be observed, with mild fever often accompanied by conjunctival hyperemia, as well as arthralgia and myalgia.

Materno-foetal transmission may occur in all trimesters of pregnancy. However, the risk of transmission with brain abnormalities in the form of microcephaly is greatest in the first trimester of pregnancy. These abnormalities result in mental retardation (which can be of greater or lesser extent), irreversible developmental disorders of varying intensity, or even death. It is therefore recommended that pregnant women perform measures to prevent sexual transmission by avoiding unprotected sexual contact with a partner who may have been infected with the Zika virus. It is also recommended that pregnant women take collective and individual protection measures to prevent mosquito bites.

Any suspected Zika virus infection during pregnancy must be addressed in an emergency obstetric consultation. Depending on the time from the onset of clinical signs, we offer:

- RT-PCR in blood until Day 7
- RT-PCR ZIKA in urine until Day 10
- Serology from Day 5

In the event of a positive result, monthly ultrasound monitoring is recommended at a multidisciplinary pre-natal diagnosis centre. Testing for Zika virus in amniotic fluid may also be offered.

At birth, RT-PCR is conducted on chord blood and urine from

the newborn.

Testing for Zika virus by PCR in blood and urine is a coded examination for health insurance reimbursement in cases with suggestive symptoms* or in patients staying in or returning from an area where the virus is circulating**, subject to the time-frames mentioned above.

** Maculopapular rash with or without fever, even moderate, and at least two of the following signs: conjunctival hyperemia, arthralgia or myalgia, in the absence of other aetiologies*

*** For information about countries where the Zika virus is in circulation, please visit: http://www.pasteur.fr/fr/institut-pasteur/presse/fiches-info/zika*