COMMENTARY

Defining Zika virus infection in pregnant women

Carlo Ticconi ^a and Giovanni Rezza^b

^aDepartment of Surgical Sciences, University Tor Vergata, Rome, Italy; ^bDepartment of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy

Zika fever, a tropical neglected disease due to a virus transmitted by *Aedes spp.* mosquito bites, became internationally known in 2016, when the WHO declared the Zika virus epidemic a global health emergency. This happened after the outbreak occurred in Brazil in 2015, that was the consequence of the introduction and spread of the virus in the Caribbean and in Latin America.

Zika fever is an acute illness clinically similar to other diseases due to mosquito-borne infections caused by flavivirus or alphaviruses circulating in tropical and sub-tropical areas of the Americas, but it may have severe consequences, such as fetal and birth defects in the offspring of infected pregnant women. The most striking feature of Congenital Zika Syndrome (CZS) is microcephaly, which is characterized by a widespread damage to the developing brain as a consequence of a specific tropism of the virus for the neural cortical progenitor cells. It has been estimated that the vertical maternal-fetal transmission rate of Zika virus is 26% and that fetal loss and CZS may occur in 14% and 21% of infected fetuses, respectively [1]. Maternal infection in the first trimester carries the highest risk of CZS, even though CZS can also develop when the mother becomes infected later in pregnancy [2]. For these reasons it is extremely important for both clinicians and epidemiologists to formulate a clear case definition of Zika virus infection in pregnancy, which is not an easy goal, since up to 80% of Zika infections are asymptomatic, and even symptomatic illness is usually mild and characterized by nonspecific clinical manifestations.

This issue has been addressed by Ximenes et al. in a recent article published in *PLoS Negl Trop Dis* in the 7th October issue [3]. In this article, the authors investigated a cohort of 694 pregnant women with rash recruited in north-east Brazil during the declining phase of the 2015–2017 epidemic. About 24% of women tested positive by quantitative reverse transcription polymerase chain reaction (qRT-PCR), but only 10% of them developed IgM antibodies within 3 months, and 48.5% had Zika-specific PRNT₅₀ (IgG) titers ≥ 20 within 90 days of rash. When applying a diagnostic algorithm to these results, 27% of the women were classified as having robust evidence, 4% moderate evidence, and 13% limited evidence of Zika

virus infection during pregnancy, while 19.5% as having an unspecified flavivirus infection. The authors concluded that combining longitudinal data obtained by the use of different methods, such as PCR and serologic testing, may slightly improve diagnostic sensitivity.

The study underlines difficulties in defining Zika virus infections in pregnant women with rash in contexts where there is a co-circulation of different flaviviruses. Indeed, serologic tests appear to have a low sensitivity but they may also have a low specificity because of cross-reactions due to previous dengue infection. Moreover, the sensitivity of molecular methods is limited by the narrow window of opportunity provided by the viremia. Repeated testing using different methods and different fluids might increase the sensitivity of the case-definition.

In conclusion, the diagnosis of Zika virus infection remains difficult due to the limits of the single assays in terms of both sensitivity and specificity. Moreover, a high proportion of cases may be asymptomatic. Thus, using multiple methods over a longer period of time, possibly starting before pregnancy, may improve the diagnostic accuracy, facilitating individual and public health decisions.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Carlo Ticconi <http://orcid.org/0000-0003-1923-2744>

References

- [1] Pomar L, Vouga M, Lambert V, et al. Maternal-fetal transmission and adverse perinatal outcomes in pregnant women infected with Zika virus: prospective cohort study in French Guiana. *BMJ*. 2018;363:k4431.
- [2] Musso D, Ko AI, Baud D. Zika virus infection – after the pandemic. *N Engl J Med*. 2019;381:1444–1457.
- [3] Ximenes RAA, Miranda-Filho DB, Brickley EB, et al. Microcephaly epidemic research group (MERG). Zika virus infection in pregnancy: establishing a case definition for clinical research on pregnant women with rash in an active transmission setting. *PLoS Negl Trop Dis*. 2019 Oct 7;13(10):e0007763.