

1 Mini-commentary on Zika virus and pregnancy

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3 **Factors relating to fetal assessment**

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12 The papers, commentaries and debates in this issue of the journal highlight a number of uncertainties
13 regarding Zika Virus in pregnancy.

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15 About 80% of Zika virus infections in adults occur without distinguishing symptoms. Whether this is true for
16 pregnant women remains unknown as is any relationship between the presence or absence of specific
17 symptoms and the risk of maternal to fetal viral transmission. The CDC documented (Armstrong et al
18 (Morbidity and Mortality Weekly Report (MMWR), March 18, 2016) that all 115 adult USA residents with
19 laboratory evidence of recent Zika virus infection reported a clinical illness. Whether symptomatic disease is
20 indeed as common as initially thought is important, but in the meantime it seems prudent to monitor at risk
21 exposed pregnant women. Although Zika serology remains imperfect and crossreactivity with other filiviruses
22 is a problem, a negative result should provide a degree of reassurance.

23 Congenital infections progress in four steps: maternal exposure; maternal infection; fetal infection and effects
24 on the fetus. How this relates to Zika infection remains unknown. In early pregnancy, disruption before
25 migration of primitive neuroectodermal cells in the ventricular zone may lead to a migration disorder
26 (Barkovich AJ et al . Brain. 2012;135:1348-69). Cellular loss, calcification and destructive lesions in later
27 pregnancy may be direct effects of infection.

28 Examination of infected newborns and fetuses is central to understanding disease progression. The effects of
29 using different charts, and utilizing a cutoff of 2 or 3 Standard Deviations below expected mean for gestation
30 when analyzing head circumference (HC) will of course have an effect on sensitivity and screen positive rates
31 (Lancet. 2016 Feb 13;387(10019):621-4). Accurate estimation of gestational age is essential, as this is crucial to
32 appropriately plot fetal or newborn head size and growth. When dating by crown rump length in the first
33 trimester is not possible, utilization of HC is obviously problematic in this scenario where it is precisely the
34 measurement that may be affected. George Saade rightly points out that fetal - compared to neonatal -
35 measurements must be interpreted with caution as here the HC is estimated indirectly. A preterm infant HC
36 growth standard—including data from Brazil- has been suggested by the World Health Organisation. Use of the
37 fetal standards on the same population would allow seamless integration of assessment from intrauterine to
38 postnatal life (Villar et al, Lancet, 2014;384: 857- 68., Papageorghiou et al, Lancet. 2014;384:869-7).

39 It is important to understand the limitations of first-level screening using HC. Microcephaly represents the end-
40 stage measurable manifestation of underlying abnormalities that affect the fetal brain. Additional imaging
41 findings associated with this infection - Intracerebral calcifications, periventricular or intraventricular
42 echogenicities and irregularly shaped lateral ventricles; callosal or vermian dysgenesis and posterior fossa
43 abnormalities such as a small transverse cerebellar diameter, enlarged cisterna magna or increased amount of
44 cerebrospinal fluid around the brain – are urgently needed. Harmonised data collection of imaging findings on
45 a large scale will enhance our understanding of this disease and may reveal more sensitive markers than
46 microcephaly per se.

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