The aim of the study by Pereira et al\(^1\) was to assess the association between prenatal ultrasonographic findings and neonatal outcomes among pregnant women with confirmed Zika virus infection. This is a follow-up study from that reported by Brasil et al\(^2\) in which, from September 2015 through May 2016, 345 pregnant women with acute illness and rash within the preceding 5 days were initially eligible. Ultimately, 182 pregnant women had a positive result confirmed by reverse-transcription polymerase chain reaction for Zika virus and were offered ultrasonographic examination, of whom 92 (51\%) opted for at least 1 second- or third-trimester ultrasonographic examination and had known neonatal outcomes. A key finding of the study is that a negative ultrasonographic result cannot be used to reassure parents that the outcome of the pregnancy will be normal.

The authors found that, when a finding well known to be associated with Zika virus infection (such as microcephaly or brain calcification) was present, the specificity for abnormal outcome was 97.9\%. However, the associated sensitivity was only 22.2\%. The authors chose to include fetal growth restriction (which can be due to causes other than Zika infection) and Blake pouch cyst (which as an isolated finding and is typically considered to be a normal variant) as Zika-associated abnormal findings. However, it is not known which of these findings were present in isolation. All pregnancies with a Zika-associated abnormal ultrasonographic finding had at least 1 ultrasonographic finding with no prior association with Zika infection, most commonly abnormal Doppler measurements.\(^1\)

There were 26 pregnancies with an isolated ultrasonographic finding that might or might not have been associated with Zika infection. However, because of the manner in which the abnormalities were reported and inconsistencies in the Appendix from the article by Brasil et al\(^2\) and the present article, it is difficult to correlate the individual nonspecific ultrasonographic findings with the associated abnormal outcomes. Some abnormalities (eg, cardiac abnormality in a fetus of a patient with diabetes) might have a cause other than Zika infection.\(^2\) However, a particularly interesting finding is that of abnormal middle cerebral artery Doppler results being associated with abnormal outcome, with 1 neonatal death occurring after the isolated finding of an abnormal middle cerebral artery Doppler examination. A larger population with Doppler studies is needed because this finding is in contrast to that of the study by Melo et al,\(^3\) in which their series of 11 patients with prenatal ultrasonographic findings suggestive of Zika infection had normal results for umbilical artery and middle cerebral artery Doppler examination.

An important finding of the study is that, in 55 pregnancies with normal prenatal ultrasonographic results, 23 (41\%) of neonates had adverse neonatal outcomes. Obviously, this type of data are needed for patient counseling. But this relatively poor negative predictive value cannot be used to counsel patients in other geographic areas (or even different study accrual dates) owing to lower disease prevalence in other regions of the world and decreased disease incidence overall. Of 2391 completed pregnancies with laboratory evidence of Zika virus infection in the 50 US states and District of Columbia as of March 31, 2018, with known pregnancy outcome, there were 116 liveborn neonates with Zika-associated birth defects (CNS abnormalities, ocular abnormalities, and hearing loss) and 9 pregnancy losses for an adverse outcome rate of 5.2\%.\(^4\) In the study by Pereira et al,\(^1\) the recruitment period was during the initial phases of the Zika virus epidemic in Brazil, when the "herd

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immunity” was low; thus, rates of primary infection were high. The incidence of Zika virus infection has decreased dramatically over the past 2 years.\(^5\) It is likely that secondary Zika virus infection does not carry the same prognosis as primary infection.\(^6\)

Another issue to consider when counseling patients is the interval between patient-reported symptoms and the performance of the ultrasonography. For example, 2 neonates with composite adverse neonatal outcomes had a single ultrasonographic scan performed less than 4 weeks after Zika virus infection, thus not necessarily allowing sufficient time for the sequelae of infection to become apparent on sonographic examination.

A final important consideration is inclusion bias. The negative predictive value found in this study is profoundly affected by the patients recruited, those who continued to participate in the study, and those who ultimately had live births with follow-up clinical care and neuroimaging. There was almost 50% attrition of the initial Zika virus–positive population. Although the authors mention that many patients declined ultrasonography because of the burden of traveling to the obstetrical facility or fear of possible fetal abnormalities, other reasons for attrition could affect their results. Patients with abnormal ultrasonographic findings from scans that were performed elsewhere might have been excluded or lost to follow-up. The bias in population is shown by the (1) pregnant women with first-trimester Zika virus infection having a lower adverse outcome rate than those infected in the second trimester (26.7% for first-trimester Zika virus infection pregnancies vs 68.9% for second-trimester Zika virus infection pregnancies), and (2) the absence of significant differences in gestational age at the time of infection between the pregnant women with vs those without abnormal results on ultrasonography. Each of these is unexpected from findings of prospective cohorts but can at least partially be explained by the exclusion of mother-neonate dyads with first-trimester pregnancy demise because they never would have had a second-trimester sonography to be included in the current study. This inclusion bias does not change the sensitivity and specificity of the ultrasonographic findings described in this study but emphasizes that these quantitative results can only be applied to a similarly acquired population and not, for example, to patients presenting with Zika virus infection in the first trimester of pregnancy.

Finally, somewhat off-setting the previously mentioned factors that would decrease the likelihood of abnormalities being present in an affected pregnancy is the limitation of ascertainment bias. This was a “real-world” study in Brazil, where it can be very difficult for patients to travel to clinics for follow-up; thus, there was great variability in postnatal testing. Of 91 liveborn neonates, only 64 had fundoscopic eye examination, 27 had their hearing tested, and 68 had neuroimaging. Thus, abnormalities could have been missed in infants without complete testing. For example, as found in the study by Aragao et al,\(^7\) even neonates without microcephaly can have findings on postnatal magnetic resonance imaging suggestive of congenital Zika virus infection. It is also likely that additional abnormalities will manifest as the cohort of infants grows to school age.

The conclusion that comprehensive postnatal evaluation is recommended for all neonates with in utero Zika virus exposure is clearly documented in this study. However, the high rates of adverse outcome in pregnancies with isolated findings nonspecific to Zika virus infection are likely not reflective of what will be found in other populations from different geographic regions and differing background rates of primary Zika virus infection.
Conflict of Interest Disclosures: None reported.

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