OBSTETRICS

Femur-sparing pattern of abnormal fetal growth in pregnant women from New York City after maternal Zika virus infection

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BACKGROUND: Zika virus is a mosquito-transmitted flavivirus, which can induce fetal brain injury and growth restriction following maternal infection during pregnancy. Prenatal diagnosis of Zika virus—associated fetal injury in the absence of microcephaly is challenging due to an incomplete understanding of how maternal Zika virus infection affects fetal growth and the use of different sonographic reference standards around the world. We hypothesized that skeletal growth is unaffected by Zika virus infection and that the femur length can represent an internal standard to detect growth deceleration of the fetal head and/or abdomen by ultrasound.

OBJECTIVE: We sought to determine if maternal Zika virus infection is associated with a femur-sparing pattern of intrauterine growth restriction through analysis of fetal biometric measures and/or body ratios using the 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project and World Health Organization Fetal Growth Chart sonographic references.

STUDY DESIGN: Pregnant women diagnosed with a possible recent Zika virus infection at Columbia University Medical Center after traveling to an endemic area were retrospectively identified and included if a fetal ultrasound was performed. Data were collected regarding Zika virus testing, fetal biometry, pregnancy, and neonatal outcomes. The 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project and World Health Organization Fetal Growth Chart sonographic standards were applied to obtain Z-scores and/or percentiles for fetal head circumference, abdominal circumference, and femur length specific for each gestational week. A novel 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project standard was also developed to generate Z-scores for fetal body ratios with respect to femur length (head circumference:femur length, abdominal circumference:femur length). Data were then grouped within clinically relevant gestational age strata (<24, 24—27 6/7, 28—33 6/7, >34 weeks) to analyze time-dependent effects of Zika virus infection on fetal size. Statistical analysis was performed using Wilcoxon signed-rank test on paired data, comparing either abdominal circumference or head circumference to femur length.

RESULTS: A total of 56 pregnant women were included in the study with laboratory evidence of a confirmed or possible recent Zika virus infection. Based on the Centers for Disease Control and Prevention definition for microcephaly after congenital Zika virus exposure, microcephaly was diagnosed in 5% (3/56) by both the 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project and World Health Organization Fetal Growth Chart standards (head circumference Z-score ≤ -2 or $\leq 2.3\%$). Using 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project, intrauterine fetal growth restriction was diagnosed in 18% of pregnancies (10/56; abdominal circumference Z-score ≤ -1.3, $<10\%$). Analysis of fetal size using the last ultrasound scan for all subjects revealed a significantly abnormal skewing of fetal biometrics with a smaller abdominal circumference vs femur length by either 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project or World Health Organization Fetal Growth Chart ($P < .001$ for both). A difference in distribution of fetal abdominal circumference compared to femur length was first apparent in the 24—27 6/7 week strata (2014 International Fetal and Newborn Growth Consortium for the 21st Century Project, $P = .002$; World Health Organization Fetal Growth Chart, $P = .001$). A significantly smaller head circumference compared to femur length was also observed by 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project as early as the 28—33 6/7 week strata (2014 International Fetal and Newborn Growth Consortium for the 21st Century Project, $P = .007$). Overall, a femur-sparing pattern of growth restriction was detected in 52% of pregnancies with either head circumference:femur length or abdominal circumference:femur length fetal body ratio <10th percentile (2014 International Fetal and Newborn Growth Consortium for the 21st Century Project Z-score ≤ -1.3).

CONCLUSION: An unusual femur-sparing pattern of fetal growth restriction was detected in the majority of fetuses with congenital Zika virus exposure. Fetal body ratios may represent a more sensitive ultrasound biomarker to detect viral injury in nonmicrocephalic fetuses that could impart long-term risk for complications of congenital Zika virus infection.

Key words: biomarker, biometry, biparietal diameter, congenital Zika virus syndrome, femur length, fetal growth restriction, fetal infection, fetus, head circumference, INTERGROWTH-21st, intrauterine growth restriction, microcephaly, pregnancy, teratogenesis, ultrasound, virus, Zika

Introduction

Zika virus (ZIKV) is a mosquito-transmitted flavivirus, recently linked to microcephaly following a maternal infection during pregnancy.[1] Vertical transmission of ZIKV has been associated with fetal microcephaly and development of the congenital ZIKV syndrome, a condition encompassing a spectrum of fetal neurologic injury including cortical malformations, ventriculomegaly, ocular injury, and arthrogryposis.[2-4] A maternal ZIKV infection has been associated with a rate of birth defects between 5—8%, but may be as high as 13% when infection occurs in the first trimester.[5,6] Recently, reports of children with a normal head

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AJOG at a Glance

Why was this study conducted?
To determine if Zika virus infection during pregnancy is associated with a femur-sparing pattern of fetal growth restriction, similar to observations in a nonhuman primate model of decelerating growth of the fetal head and abdomen with respect to femur length.

Key findings
An unusual femur-sparing pattern of fetal growth restriction was detected in the majority of fetuses with congenital Zika virus exposure using 2014 International Fetal and Newborn Growth Consortium for the 21st Century Project fetal body ratios comparing head or abdominal circumference to femur length.

What does this add to what is known?
Fetal body ratios may provide a new screening tool to detect Zika virus-associated fetal injury in pregnancies without overt microcephaly.

circumference (HC) at birth who were later found to have abnormal brain imaging, ocular injury, and postnatal development of microcephaly, has led to the concept that microcephaly does not capture the broader spectrum of ZIKV-associated brain injury.[3,7-10] Identification of fetuses with a normal head size that are at risk for long-term adverse outcomes remains limited due to the incomplete knowledge of how a less overt spectrum of ZIKV-associated fetal injury may be detected prenatally. This limitation is further compounded by weaknesses related to diagnostic testing including: (1) inadequate availability of ZIKV testing in regions at risk, (2) lower sensitivity of real-time polymerase chain reaction testing due to the transient nature of ZIKV viremia, and (3) lower positive predictive value of serologic testing due to cross-reactivity between ZIKV and related flaviviruses.

In a nonhuman primate model, ZIKV-associated fetal brain injury was associated with an unusual femur-sparing profile of intrauterine growth restriction (IUGR) notable for a growth arrest in ultrasound biometric measures of the fetal head (biparietal diameter [BPD]) and abdomen (abdominal circumference [AC]) with continued growth of the femur (femur length [FL]).[11,12] This profile of IUGR has been noted as "femur-sparing,"[13] but has not been characterized in a clinical study nor is it part of the mainstream categories for IUGR; typically, IUGR has been defined as asymmetric (conserved head growth with lagging growth of the abdomen) or symmetric (equal growth restriction of the head, abdomen, and femur).[14]

There is a paucity of data to link aberrant fetal growth in the context of a maternal ZIKV infection to long-term adverse outcomes in the neonate, but IUGR may represent a sensitive indicator of viral injury to the placenta or fetus itself. Whether fetuses exposed to ZIKV with abnormal growth patterns, without microcephaly, may be more susceptible to eye injury or late-onset microcephaly is unknown and represents an important knowledge gap.[15] Although IUGR has been reported in pregnant women with a possible ZIKV infection, the profile of IUGR has not been described.[2,10] Our objective was to determine if maternal ZIKV infection was associated with a femur-sparing profile of growth restriction, similar to observations in a nonhuman primate model of congenital ZIKV infection.[11,12] Such an observation may be a first step in identifying non-microcephalic fetuses at risk for long-term morbidity.

Materials and Methods

Study population and ethics statement

All pregnant women presenting to Columbia University Medical Center from Jan. 1, 2016, through Feb. 1, 2017, from an area with known ZIKV local transmission were offered screening per Centers for Disease Control and Prevention (CDC) recommendations. The Columbia University Institutional Review Board approved the study (IRB-AAAQ9686) as a retrospective chart review and informed consent was not required. Cases were excluded if no ultrasound for fetal size or anatomy was completed prior to delivery. The gestational age and due date were estimated according to methods recommended by the American Congress of Obstetricians and Gynecologists.[16] Following ZIKV diagnosis, a pregnancy ultrasound was performed, and repeated every 3–4 weeks, for the duration of the pregnancy. Timing of ZIKV exposure was estimated based on maternal travel history, but could have occurred later in pregnancy due to sexual exposure from an infected partner; therefore, we included 4 subjects with immediate preconception exposure. Neonatal outcomes were assessed through measurement of a postnatal HC and head ultrasound scan in the first week of life. A more comprehensive assessment of outcomes was not possible due to limitations on our institutional human subject's approval and the challenge of data procurement from multiple private pediatric clinics in New York, NY; therefore, results for some recommended neonatal screening tests were not obtained.

ZIKV diagnosis

Based on uncertainties in the diagnostic testing for ZIKV infection, we followed CDC convention to describe women as having a "possible" ZIKV infection based on: (1) ZIKV infection detected by RNA testing on maternal, placental, or fetal specimen; or (2) diagnosis of ZIKV infection or unspecified flavivirus infection, timing of infection cannot be determined (ie, positive/equivocal ZIKV IgM and ZIKV plaque reduction neutralization test [PRNT] titer $\geq$10, regardless of dengue virus PRNT value; or negative ZIKV IgM, and positive or equivocal dengue virus IgM, and ZIKV PRNT titer $\geq$10, regardless of dengue virus PRNT titer).[17,18] We also followed CDC guidance for the interpretation of laboratory testing of the infant for evidence of congenital ZIKV infection.[17]

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