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Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy

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IMPORTANCE Understanding the risk of birth defects associated with Zika virus infection during pregnancy may help guide communication, prevention, and planning efforts. In the absence of Zika virus, microcephaly occurs in approximately 7 per 10 000 live births.

OBJECTIVE To estimate the preliminary proportion of fetuses or infants with birth defects after maternal Zika virus infection by trimester of infection and maternal symptoms.

DESIGN, SETTING, AND PARTICIPANTS Completed pregnancies with maternal, fetal, or infant laboratory evidence of possible recent Zika virus infection and outcomes reported in the continental United States and Hawaii from January 15 to September 22, 2016, in the US Zika Pregnancy Registry, a collaboration between the CDC and state and local health departments.

EXPOSURES Laboratory evidence of possible recent Zika virus infection in a maternal, placental, fetal, or infant sample.

MAIN OUTCOMES AND MEASURES Birth defects potentially Zika associated: brain abnormalities with or without microcephaly, neural tube defects and other early brain malformations, eye abnormalities, and other central nervous system consequences.

RESULTS Among 442 completed pregnancies in women (median age, 28 years; range, 15-50 years) with laboratory evidence of possible recent Zika virus infection, birth defects potentially related to Zika virus were identified in 26 (6%; 95% CI, 4%-8%) fetuses or infants. There were 21 infants with birth defects among 395 live births and 5 fetuses with birth defects among 47 pregnancy losses. Birth defects were reported for 16 of 271 (6%; 95% CI, 4%-9%) pregnant asymptomatic women and 10 of 167 (6%; 95% CI, 3%-11%) symptomatic pregnant women. Of the 26 affected fetuses or infants, 4 had microcephaly and no reported neuroimaging, 14 had microcephaly and brain abnormalities, and 4 had brain abnormalities without microcephaly; reported brain abnormalities included intracranial calcifications, corpus callosum abnormalities, abnormal cortical formation, cerebral atrophy, ventriculomegaly, hydrocephaly, and cerebellar abnormalities. Infants with microcephaly (18/442) represent 4% of completed pregnancies. Birth defects were reported in 9 of 85 (11%; 95% CI, 6%-19%) completed pregnancies with maternal symptoms or exposure exclusively in the first trimester (or first trimester and periconceptional period), with no reports of birth defects among fetuses or infants with prenatal exposure to Zika virus infection only in the second or third trimesters.

CONCLUSIONS AND RELEVANCE Among pregnant women in the United States with completed pregnancies and laboratory evidence of possible recent Zika infection, 6% of fetuses or infants had evidence of Zika-associated birth defects, primarily brain abnormalities and microcephaly, whereas among women with first-trimester Zika infection, 11% of fetuses or infants had evidence of Zika-associated birth defects. These findings support the importance of screening pregnant women for Zika virus exposure.

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Editorial
Supplemental content

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Zika virus infection during pregnancy can cause microcephaly and brain abnormalities[1]; however, the magnitude of risk is unknown. For first-trimester maternal Zika virus infection, modeling of data from French Polynesia suggested about a 1% risk of microcephaly, and a model based on a Zika outbreak in Bahia, Brazil, suggested a risk between 1% and 13%.[2,3] Additionally, available data suggest that most Zika virus infections cause mild symptoms and many are asymptomatic.[4] Although microcephaly following asymptomatic Zika virus infection has been reported,[5-9] most published reports have documented the risk of microcephaly, brain abnormalities, and other adverse outcomes among pregnant women with symptomatic Zika virus disease.[8,10-12] It is unclear if this is because some asymptomatic pregnant women with travel or sexual exposure to Zika virus are not tested or if women who experience symptomatic Zika virus disease are more likely to have adverse pregnancy outcomes.

This report describes the US Zika Pregnancy Registry (USZPR) and the proportion of fetuses or infants with birth defects potentially associated with maternal Zika virus infection among women in the USZPR and evaluates whether the proportion with birth defects differs based on the presence of maternal symptoms of Zika virus infection or by trimester of possible infection.

Key Points

Question What proportion of fetuses and infants of women in the United States with laboratory evidence of possible Zika virus infection during pregnancy have birth defects?

Findings Based on preliminary data from the US Zika Pregnancy Registry, among 442 completed pregnancies, 6% overall had a fetus or infant with evidence of a Zika virus–related birth defect, primarily microcephaly with brain abnormalities, whereas among women with possible Zika virus infection during the first trimester, 11% had a fetus or infant with a birth defect.

Meaning These findings support the importance of screening pregnant women for Zika virus exposure.

Methods

In collaboration with state, tribal, territorial, and local health departments, the Centers for Disease Control and Prevention (CDC) established the USZPR as an enhanced surveillance system to monitor pregnancy and fetal or infant outcomes among pregnant women and fetuses or infants with laboratory evidence of possible Zika virus infection to assess the proportion of birth defects occurring in infants following maternal to fetal transmission of Zika virus infection.[13,14] In accordance with federal human subjects protection regulations at 45 CFR §46.101c and §46.102d and with the Guidelines for Defining Public Health Research and Public Health Non-Research, the USZPR was reviewed by a human subjects protection coordinator at the National Center for Emerging and Zoonotic Infectious Diseases of the CDC and in numerous jurisdictions and determined to be a nonresearch, public health surveillance activity exempt from institutional review board evaluation. All data reported to the CDC on pregnancies and fetal or infant outcomes potentially related to Zika virus infections are protected by an Assurance of Confidentiality (http://www.cdc.gov/od/science/integrity/confidentiality/).

The USZPR includes data from all US states, the District of Columbia, and all US territories except Puerto Rico; pregnancies in Puerto Rico are monitored separately by the Zika Active Pregnancy Surveillance System.[13,15] Since February 5, 2016, the CDC has recommended Zika virus testing for all pregnant women who have possible exposure to Zika virus through travel, sexual contact, or local mosquito transmission regardless of symptoms.[16] For this report, data from the USZPR were limited to pregnancies completed in the continental United States or Hawaii from December 2015 through September 22, 2016, and reported to the CDC from January 15, 2016, through September 22, 2016, including reports from pregnancies completed before the USZPR was established. Information for the completed pregnancies reported by September 22, 2016, was updated with additional data on these pregnancies reported to USZPR through November 10, 2016. Not included in this report are an additional 229 completed pregnancies reported to the USZPR as of November 10, 2016; complete information on key variables is not yet available for many of these recently completed pregnancies.

Completed pregnancies included those that ended in a spontaneous abortion, termination of pregnancy, stillbirth, or live-born infant; ongoing pregnancies were excluded from this report. Pregnancies can be reported to the USZPR at any point during pregnancy or postnatally; some women are tested for Zika virus infection after concerns about adverse fetal or infant effects have been noted. Most reports to the USZPR are submitted from state and local health departments. This report includes data from 9 pregnant travelers with completed pregnancies whose outcomes were reported previously and from 5 pregnant women reported to have persistent detection of Zika virus RNA.[14,17]

To meet inclusion criteria for the USZPR, either the mother, the placenta, or the fetus or infant must have had laboratory evidence of possible Zika virus infection. For this analysis, maternal samples included urine, serum, and amniotic fluid; fetal or infant samples included urine, serum, cerebrospinal fluid, umbilical cord, or any fetal tissue; and placental samples were assessed separately. Laboratory evidence of possible Zika virus infection included (1) presence of Zika virus RNA on real-time reverse transcription-polymerase chain reaction (rRT-PCR) test or other nucleic acid amplification test; (2) maternal serological evidence of a recent Zika virus infection based on a positive or equivocal result on the Zika virus IgM antibody capture enzyme-linked immunosorbent assay (http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika) with a Zika virus plaque reduction neutralization testing (PRNT) titer greater than or equal to 10 and either a negative dengue IgM or a dengue PRNT less than 10 or both; (3) maternal serological evidence of a recent unspecified flavivirus infection, based on positive or equivocal Zika virus IgM results and PRNT titers greater than or equal to 10 for both Zika virus and another

flavivirus (eg, dengue); (4) serological evidence of a recent Zika virus infection in an infant based on positive or equivocal Zika virus IgM results; and (5) placenta or other tissue samples with immunohistochemistry staining indicative of Zika virus infection or presence of Zika virus RNA by RT-PCR.[13,18-21] These laboratory inclusion criteria were specified as "possible" Zika virus infection because in addition to those with laboratory confirmed Zika virus, the USZPR also includes mother-infant pairs with serological evidence of a recent unspecified flavivirus infection.

The gestational timing of Zika virus infection for symptomatic pregnant women was based on maternal report of date of symptom onset; for asymptomatic pregnant women, timing was based on the trimester of exposure (travel to an area of active Zika virus transmission or sexual exposure). The most common symptoms of Zika virus infection are fever, rash, arthralgia, and conjunctivitis.[4] The estimates for the proportion with birth defects for first-trimester infection were based on pregnant women with symptoms in the first trimester of pregnancy or asymptomatic pregnant women with exposure to Zika virus infection only in the first trimester of pregnancy. Periconceptional exposures were defined as exposure in the 4 weeks before the last menstrual period and through the first 2 weeks after the last menstrual period. Pregnant women with exposure in the periconceptional period and first trimester were classified as having first-trimester exposure; those with multiple trimesters of exposure including the periconceptional period were classified by their trimester of exposure. Risk among asymptomatic pregnant women with exposure in an area of active Zika virus transmission during more than 1 trimester, including the first trimester, was assessed separately from those with known dates of infection.

Birth defects potentially associated with Zika virus infection during pregnancy (referred to as "birth defects" throughout) included brain abnormalities with or without microcephaly, neural tube defects and other early brain malformations, eye abnormalities, and other consequences of central nervous system dysfunction including arthrogryposis (joint contractures), clubfoot, congenital hip dysplasia, and congenital deafness (**Box** and eTable in the Supplement). The included birth defects were based primarily on case reports of outcomes occurring in association with Zika virus infection during pregnancy; there is more evidence for some of these birth defects than for others, and a causal link has not been established for all.[5,10,12,21-27] Because much of the focus to date has been on microcephaly and brain abnormalities, data were summarized in 2 mutually exclusive categories: (1) brain abnormalities with or without microcephaly regardless of the presence of additional birth defects and (2) neural tube defects and other early brain malformations, eye abnormalities, and other consequences of central nervous system dysfunction among those without evident brain abnormalities or microcephaly. Clinical experts reviewed reported information to ensure each infant with birth defects met the above criteria. Among fetuses with birth defects, spontaneous abortions (<20 weeks' gestation), stillbirths (≥20 weeks' gestation), and terminations of pregnancy were grouped together as pregnancy losses, a subset of completed pregnancies.

Box. Birth Defects Potentially Related to Zika Virus Infection During Pregnancy and Monitored by the US Zika Pregnancy Registry for Enhanced Surveillance

Brain Abnormalities With and Without Microcephaly

Confirmed or possible congenital microcephaly[a]

Intracranial calcifications

Cerebral atrophy

Abnormal cortical formation (eg, polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia)

Corpus callosum abnormalities

Cerebellar abnormalities

Porencephaly

Hydranencephaly

Ventriculomegaly/hydrocephaly (excluding "mild" ventriculomegaly without other brain abnormalities)

Fetal brain disruption sequence (collapsed skull, overlapping sutures, prominent occipital bone, scalp rugae)

Other major brain abnormalities including intraventricular hemorrhage in utero (excluding postnatal intraventricular hemorrhage)

Neural Tube Defects and Other Early Brain Malformations

Neural tube defects including anencephaly, acrania, encephalocele, spina bifida

Holoprosencephaly (arhinencephaly)

Eye Abnormalities

Microphthalmia/anophthalmia

Coloboma

Cataract

Intraocular calcifications

Chorioretinal anomalies involving the macula (eg, chorioretinal atrophy and scarring, macular pallor, gross pigmentary mottling and retinal hemorrhage; excluding retinopathy of prematurity)

Optic nerve atrophy, pallor, and other optic nerve abnormalities

Consequences of Central Nervous System Dysfunction

Congenital contractures (eg, arthrogryposis, clubfoot, congenital hip dysplasia) with associated brain abnormalities

Congenital deafness documented by postnatal audiological testing

[a] Live births: measured head circumference (adjusted for gestational age and sex) less than the third percentile at birth or, if not measured at birth, within first 2 weeks of life. Pregnancy loss: prenatal head circumference more than 3 SDs below the mean based on ultrasound or postnatal head circumference less than the third percentile. Birth measurements are evaluated using the Intergrowth-21st standards (http://intergrowth21.ndog.ox.ac.uk/) based on measurements within 24 hours of birth.

Among completed pregnancies, all fetuses or infants with one of these birth defects were included as the numerator in the preliminary estimates with outcomes for multiple gestation pregnancies counted once; the denominator was all completed pregnancies with and without birth defects. The proportion affected by birth defects was calculated as the number of fetuses or infants with birth defects among the total completed pregnancies, and the 95% confidence interval for a binomial proportion was estimated using the Wilson score interval.[28] All analyses were performed using SAS software version 9.3 (SAS Institute Inc), except for the confidence

intervals for proportions, which were calculated in OpenEpi version 3.01. Data were reported as proportions rather than risk estimates because of the preliminary nature of the data and potential selection bias. Separate estimates were made for asymptomatic and symptomatic pregnant women and by trimester of infection. Reports to the USZPR were summarized by laboratory evidence of Zika virus infection.

Sensitivity analyses were conducted to assess the effect of potential biases in the completed pregnancies and fetuses or infants with birth defects reported to the CDC either (1) retrospectively during early 2016 including reports of pregnancies and adverse outcomes that occurred prior to regular weekly reporting from the jurisdictions to the USZPR because these reports might have disproportionately included adverse outcomes or (2) with future or very recent estimated dates of delivery (EDD) because some pregnancy losses could potentially be associated with the occurrence of birth defects. The sensitivity analysis included only completed pregnancies with an EDD from April 2016 through August 2016; the sensitivity analysis was completed for pregnancies with any trimester of infection and specifically for pregnancies with symptoms or exposure exclusively in the first trimester (or first trimester and periconceptional period).

Results

A total of 442 pregnant women (median age, 28 years; range, 15-50 years) in the USZPR with possible Zika virus infection met inclusion criteria and had completed pregnancies. Among these women, 271 (61%) were asymptomatic, 167 (38%) were symptomatic, and 4 (1%) had missing information on symptom status. All pregnant women with completed pregnancies included in this report had travel-associated Zika virus infections, meaning the infection was acquired in US territories or outside the United States or through sexual contact with a traveler; 4 were presumed to be the result of sexual transmission in a nontraveler.

Among the 442 completed pregnancies, there were 26 fetuses or infants (6%; 95% CI, 4%-8%) with birth defects, including 21 infants with birth defects among 395 live births and 5 fetuses with birth defects among 47 pregnancy losses (spontaneous abortions, pregnancy terminations, and stillbirths). Twenty-two (85%) of these fetuses or infants had brain abnormalities, microcephaly, or both. These 22 fetuses or infants included 4 with microcephaly and no reported neuroimaging, 14 with microcephaly and brain abnormalities, and 4 with brain abnormalities without a finding of microcephaly. Reported brain abnormalities included intracranial calcifications, corpus callosum abnormalities, abnormal cortical formation, cerebral atrophy, ventriculomegaly, hydrocephaly, and cerebellar abnormalities. Eleven of the 22 fetuses or infants had intracranial calcifications with or without other brain abnormalities. Among the 4 with birth defects who did not have evident brain abnormalities or microcephaly, 2 had encephalocele, 1 had eye abnormalities, and 1 had hearing abnormalities. The 18 infants with a finding of microcephaly represent 4% (18/442) of the completed pregnancies. The 26 cases of birth defects occurred among fetuses or infants of pregnant women with Zika virus exposure in the following countries with active Zika virus transmission during their pregnancies: Barbados, Belize, Brazil, Colombia, Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Mexico, Republic of Marshall Islands, and Venezuela.

The proportion of fetuses or infants with birth defects by maternal symptom status was 6% (95% CI, 4%-9% [16/271]) for asymptomatic women and 6% (95% CI, 3%-11% [10/167]) for symptomatic women (**Table 1**). Among 85 pregnancies with symptom onset or exposure to Zika virus infection exclusively during the first trimester (or first trimester and periconceptional period), 9 presented with birth defects (11%; 95% CI, 6%-19%). Among 211 completed pregnancies for women with possible Zika virus exposure spanning multiple trimesters including the first trimester, 15 presented with birth defects (7%; 95% CI, 4%-11%). No birth defects were reported among the pregnancies with maternal symptoms or exposure only in the second trimester (0%; 95% CI, 0%-5% [0/76]) or third trimester (0%; 95% CI, 0%-11% [0/31]), but there are insufficient data to adequately estimate the proportion affected during these trimesters (Table 1). Gestational timing of infection was unknown for 2 of the 26 fetuses or infants with birth defects and 27 of the total completed pregnancies.

Most maternal samples had serological evidence of a recent Zika virus infection or a recent unspecified flavivirus infection (**Table 2** and **Table 3**). The majority of mother-infant pairs included in the USZPR had laboratory evidence based only on maternal samples (360/442); 49 (11%) demonstrated presence of Zika virus in the placenta and 161 had negative results on placental testing. Approximately 41% (182/442) of all infants did not have Zika virus testing. Some mother-infant pairs had negative test results for maternal, placental, or fetal or infant samples but met the inclusion criteria based on at least 1 sample type.

In the sensitivity analysis limiting the reports to completed pregnancies with an EDD from April through August 2016, the proportion with birth defects was comparable with the overall analysis, with 22 fetuses or infants presenting with birth defects among 309 completed pregnancies (7%; 95% CI, 5%-11%). This subanalysis excluded 26 completed pregnancies (1 with birth defects) with missing information on EDD, 21 completed pregnancies (1 with birth defects) with an EDD from December 2015 through March 2016, and 86 completed pregnancies (2 with birth defects) with an EDD in September 2016 or later.

In the sensitivity analysis limiting the reports to completed pregnancies with symptom onset or exposure exclusively during the first trimester (or first trimester and periconceptional period) and an EDD from April 2016 through August 2016, the proportion with birth defects was comparable with the overall analysis, with 7 fetuses or infants presenting with birth defects among 49 completed pregnancies (14%; 95% CI, 7%-27%), comparable with the 11% observed in the primary analysis. This subanalysis excluded 4 completed pregnancies with missing information on EDD, none of which had a fetus or infant with a birth defect; 3 completed pregnancies with an

Table 1. Pregnancy Outcomes for 442 Women With Completed Pregnancies With Laboratory Evidence of Possible Zika Virus Infection by Maternal Symptom Status and Timing of Symptom Onset or Exposure, US Zika Pregnancy Registry, December 2015–September 2016[a]

	No. of Pregnancies				
	Brain Abnormalities and/or Microcephaly[b]	Neural Tube Defects, Eye Abnormalities, and Consequences of Central Nervous System Dysfunction[c]	Total With ≥1 Birth Defect	Total Completed Pregnancies	Preliminary Estimates of Pregnancies With Birth Defects, % (95% CI)[d]
By maternal symptom status					
Maternal symptoms of Zika virus infection	8	2	10	167	6 (3-11)
No reported maternal symptoms of Zika virus infection	14	2	16	271	6 (4-9)
Unknown symptom status	0	0	0	4	
By timing of symptoms or exposure					
First trimester	8	1	9	85	11 (6-19)
Multiple trimesters including first trimester	13	2	15	211	7 (4-11)
Second trimester only	0	0	0	76	0 (0-5)
Multiple trimesters including second and third trimester	0	0	0	5	
Third trimester only	0	0	0	31	0 (0-11)
Periconceptional	0	0	0	7	
Unknown or missing data	1	1	2	27	
Total	22	4	26	442	6 (4-8)

[a] Pregnancies include live births, spontaneous abortions, terminations, and stillbirths. Outcomes for multiple-gestation pregnancies are counted once. Maternal, placental, or fetal or infant laboratory evidence of possible Zika virus infection is based on presence of Zika virus RNA on real-time reverse transcription–polymerase chain reaction or similar test, serological evidence of a recent Zika virus infection, serological evidence of a recent unspecified flavivirus infection, or immunohistochemistry staining in tissue indicating Zika virus.

[b] Includes all fetuses or infants with either microcephaly and/or brain abnormalities with or without the presence of additional birth defects; the 22 fetuses or infants included 4 with microcephaly and no reported neuroimaging, 14 with microcephaly and brain abnormalities reported, and 4 with brain abnormalities reported without a finding of microcephaly.

[c] Report of one of these birth defects in an infant with no report of brain abnormalities and/or microcephaly; the 4 fetuses or infants included 2 with encephalocele, 1 with eye abnormalities, and 1 with hearing abnormalities.

[d] Ninety-five percent confidence interval for a binomial proportion using Wilson score interval.

Table 2. Summary of Samples Providing Laboratory Evidence of Possible Zika Virus Infection for 442 Women With Completed Pregnancies in the United States Reported to the US Zika Pregnancy Registry, December 2015–September 2016[a]

Maternal Specimen With Laboratory Evidence of Zika Virus or Recent Zika Virus Infection or Unspecified Flavivirus Infection	Placental Specimen With Laboratory Evidence of Zika Virus Infection	Fetal or Infant Specimen With Laboratory Evidence of Zika Virus or Recent Zika Virus Infection or Unspecified Flavivirus Infection	Fetuses or Infants With Birth Defects Potentially Linked to Congenital Zika Virus Infection, No.[b]	Completed Pregnancies, No.
Yes	Yes	Yes	6	19
Yes	Yes	No or not tested	0	20
Yes	No or not tested	Yes	8	29
No or not tested	Yes	Yes	1	3
Yes	No or not tested	No or not tested	5	360
No or not tested	Yes	No or not tested	3	7
No or not tested	No or not tested	Yes	3	4
Total No. with positive result: 428	Total No. with positive result: 49	Total No. with positive result: 55	Total: 26	Total: 442

[a] Includes live births, spontaneous abortions, terminations, and stillbirths.

[b] See the Box for a complete list of birth defects potentially associated with congenital Zika virus.

EDD from December 2015 through March 2016, including 1 fetus or infant with a birth defect; and 29 completed pregnancies with an EDD in September 2016 or later, including 1 fetus or infant with a birth defect.

Discussion

In this report based on preliminary data for pregnant women in the USZPR with laboratory evidence of possible Zika virus infection, 6% overall had a fetus or infant with evidence of a Zika-related birth defect, and among women with timing of possible Zika infection exclusively during the first trimester, 11% had a fetus or infant with a birth defect. The birth defects primarily involved included microcephaly with brain abnormalities, such as intracranial calcifications. Preliminary estimates from the USZPR were within the range of 1% to 13% risk of microcephaly following first-trimester maternal Zika virus infection modeled on the outbreak in Bahia, Brazil, lending support to the credibility of these estimates.[3]

Table 3. Summary of Laboratory Evidence of Possible Zika Virus Infection for 26 Fetuses or Infants With Birth Defects Among 442 Women With Completed Pregnancies in the United States Reported to the US Zika Pregnancy Registry, December 2015–September 2016[a]

	Fetuses or Infants With Birth Defects Potentially Linked to Congenital Zika Virus Infection, No.[b]	Completed Pregnancies, No.
Maternal test results[c]		
Zika virus infection on rRT-PCR	4	67
Serological evidence of recent Zika virus or unspecified flavivirus infection[d]	18	398
Maternal samples negative on rRT-PCR, IgM[e]	7	13
No maternal samples tested[e]	0	1
Placental test results (frozen or fixed)[c]		
Zika virus on RT-PCR	10	48
Immunohistochemistry staining demonstrating Zika virus infection in placental tissue	0	4
Placental samples negative on RT-PCR, immunohistochemistry staining[f]	10	161
No placental samples tested[f]	6	232
Fetal or infant test results[c]		
Zika virus on rRT-PCR	6	28
Serological evidence of recent Zika virus infection[g]	15	33
Immunohistochemistry staining demonstrating Zika virus infection in fetal tissue	1	3
Fetal or infant samples negative on rRT-PCR, immunohistochemistry staining[h]	5	205
No fetal or infant samples tested[h]	3	182
Total	26	442

Abbreviations: RT-PCR, conventional reverse–transcription polymerase chain reaction; rRT-PCR, real-time reverse transcription–polymerase chain reaction.

[a] Includes live births, spontaneous abortions, terminations, and stillbirths.

[b] See the Box for a complete list of birth defects potentially associated with congenital Zika virus.

[c] Individuals can be included in multiple rows depending on what tests were reported.

[d] Serological evidence of a recent Zika virus infection based on a positive or equivocal result on the Zika virus IgM with a Zika virus plaque reduction neutralization testing (PRNT) titer greater than or equal to 10 and either a negative dengue IgM or a dengue PRNT titers less than 10 or both, or serological evidence of a recent unspecified flavivirus infection based on positive or equivocal Zika virus IgM results and PRNT titers greater than or equal to 10 for both Zika virus and another flavivirus.

[e] All of these cases had infant or placental samples with laboratory evidence of possible Zika virus.

[f] Only the maternal or infant samples had laboratory evidence of possible Zika virus.

[g] Serological evidence of a recent Zika virus infection based on a positive or equivocal Zika virus IgM result.

[h] All of these cases had maternal or placental samples with laboratory evidence of possible Zika virus.

In the current report, there were no reports of birth defects among fetuses or infants with prenatal exposure to Zika virus infection only in the second trimester (0%; 95% CI, 0%-5%) or third trimester (0%; 95% CI, 0%-11%); however, the confidence intervals demonstrated the imprecision of these estimates based on current data. In addition, nearly half of the women in the USZPR had exposure during multiple trimesters of pregnancy, limiting the ability to assess timing of infection beyond the first trimester in relation to outcomes. The findings in this report emphasize the need for pregnant women to avoid travel to areas with active Zika virus transmission and consistently and correctly use condoms to prevent sexual transmission throughout pregnancy if their partner has recently traveled to an area of active Zika virus transmission.

Based on data from population-based birth defects surveillance programs for 2009-2013, the median prevalence of microcephaly in the United States was approximately 7 per 10 000 live births.[29] There are no published estimates of the prevalence of the birth defects potentially related to Zika virus infection during pregnancy combined. Among completed pregnancies in the USZPR, 6% overall were affected by 1 or more of these defects and 4% had a finding of microcephaly; this prevalence is substantially higher than the background prevalence of microcephaly.

In this study, the proportion of completed pregnancies affected by birth defects was similar following either symptomatic Zika virus disease or asymptomatic infection during pregnancy. Most reported birth defects were among fetuses or infants of women with symptoms or exposure (for those with asymptomatic infection) in the first trimester of pregnancy or in multiple trimesters including the first trimester, but timing of infection was unknown for several pregnancies. The sensitivity analysis resulted in similar estimates when the completed pregnancies were limited to those with EDDs from April through August 2016 for both all completed pregnancies and those with symptom onset or exposure exclusively in the periconceptional period or first trimester, suggesting that the estimates based on total reports are not unduly biased.

The CDC's guidance recommends Zika virus testing for all women with possible exposure during pregnancy, regardless of symptoms.[16] The findings that there were similar proportions with birth defects among those with symptomatic and asymptomatic maternal infections supports the importance of screening all pregnant women for Zika virus exposure and testing in accordance with CDC guidance. If 80% of all Zika virus infections are presumed to be asymptomatic,[4] then the 61% of completed pregnancies reported to the USZPR with asymptomatic infection might represent underascertainment of asymptomatic infections. In addition, serological testing results can be difficult to interpret in persons with other prior or recent flavivirus infections (eg, dengue), further complicating the diagnosis of Zika virus infection. Some of the pregnant women in the USZPR with recent unspecified flavivirus infection might actually have been infected with dengue virus.[30] Although mother to fetal transmission of dengue virus is presumed to be uncommon, the potential

association between congenital dengue virus infection and adverse birth outcomes is unclear.[31] In addition, prior dengue virus infection might be a cofactor that could affect the risk of adverse birth outcomes following Zika virus infection during pregnancy.[32]

The CDC's guidance for the evaluation of infants with possible congenital Zika virus infection was initially released in January 2016 and has been updated twice, most recently in August 2016.[33] Guidance currently recommends testing of the infant when there is laboratory evidence of possible maternal Zika virus infection. Guidance further recommends to consider testing in situations in which there is maternal exposure during pregnancy to Zika virus infection and no maternal testing was done or when maternal testing results were negative but testing was conducted outside the period when molecular and serological testing results would be expected to be positive. It is concerning that 3 (12%) of 26 infants with birth defects and 182 (41%) of all 442 fetuses or infants from completed pregnancies had no reported testing of fetal or infant samples. This lack of reported testing could have been due to short-term delays in obtaining testing and test results; a critical issue is ensuring that pediatric clinicians are aware of maternal Zika virus exposure or testing results and thus can readily identify infants who should be tested. More research is needed to define optimal testing strategies for identifying congenitally infected infants; some infants with evidence of congenital Zika virus infection prenatally and evidence of Zika virus in fetal tissue have negative results on cord blood samples by both PCR and IgM.[34]

Eighty-five percent of the fetuses or infants with potentially Zika-associated birth defects in this report had brain abnormalities or microcephaly, with most having both microcephaly and specific brain abnormalities. Although much of the attention has focused on microcephaly, the underlying brain abnormalities, particularly those not easily detectable on clinical assessment of the newborn, are of paramount concern. For example, case reports have highlighted the potential for underlying brain abnormalities such as ventriculomegaly among normocephalic infants with prenatal Zika virus exposure. More complete clinical evaluation of infants including neuroimaging and audiological, ophthalmological, neurological, and developmental assessments will be needed to fully describe the extent of brain abnormalities and other adverse outcomes in affected fetuses or infants.[34,35]

There are important limitations to consider. First, selection bias in who is included in the USZPR is possible, and the exact gestational timing of Zika virus infection is not known for many of the included women. Pregnant women with symptoms of Zika virus infection were presumably more likely to be tested than asymptomatic women; thus, infection ascertainment was likely more complete among those with symptoms.

Second, pregnant women with a history of possible exposure to Zika virus through travel or sex might have been more likely to be tested for Zika virus infection if fetal abnormalities were detected prenatally or if they delivered an infant with a birth defect. Therefore, identification of infections among pregnancies with abnormalities was likely higher than among pregnancies with unremarkable prenatal or postnatal findings; the USZPR does not have adequate data with which to quantify this potential bias. Conversely, birth defects might not have been completely ascertained among pregnancy losses including stillbirths; thus, birth defects might be underestimated.

Third, we cannot enumerate the number of completed pregnancies or fetuses or infants with or without birth defects that have not yet been reported to the USZPR; therefore, these preliminary estimates might overestimate the proportion affected by birth defects if completed pregnancies with adverse outcomes were reported to the USZPR more promptly than those with apparently normal outcomes.

Fourth, laboratory diagnostics currently do not identify pregnant women who were infected early in pregnancy but were tested later in pregnancy, at a time when viral RNA was no longer present and Zika virus IgM had waned. Because of the timing of infection and testing or limitations of current laboratory tests for Zika virus in mothers and infants, an infant with Zika-associated birth defects born to a mother who tested negative might have also tested negative or not have been tested, and Zika virus may never be identified as the potential cause of those defects.

Fifth, some mother-infant pairs demonstrated laboratory evidence of an unspecified flavivirus infection; therefore, some of these might not have had Zika virus infections. Sixth, the preliminary data reported to the USZPR include very little demographic information and incomplete information on other potential risk factors for birth defects. Finally, there are other causes of microcephaly, brain abnormalities, and other birth defects, including genetic and infectious causes, about which the USZPR has limited information.[36-38]

Longitudinal monitoring of the infants with possible congenital Zika virus infection is essential to fully characterize the outcomes. There are some reports of normocephalic infants with congenital Zika virus infection who have abnormal postnatal brain development or adverse effects that are not immediately apparent at birth.[11,39] In addition, future observations can elucidate the possible role of Zika virus infection in other outcomes, including spontaneous abortions and stillbirths as well as other structural birth defects that are not currently part of the inclusion criteria for Zika-associated birth defects surveillance.

Conclusion

Among pregnant women in the United States with completed pregnancies and laboratory evidence of possible recent Zika infection, 6% of fetuses or infants had evidence of Zika-associated birth defects, primarily brain abnormalities and microcephaly, whereas among women with first-trimester Zika infection, 11% of fetuses or infants had evidence of Zika-associated birth defects. These findings support the importance of screening pregnant women for Zika virus exposure.

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