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Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas

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ABSTRACT

BACKGROUND

The risk of congenital neurologic defects related to Zika virus (ZIKV) infection has ranged from 6 to 42% in various reports. The aim of this study was to estimate this risk among pregnant women with symptomatic ZIKV infection in French territories in the Americas.

METHODS

From March 2016 through November 2016, we enrolled in this prospective cohort study pregnant women with symptomatic ZIKV infection that was confirmed by polymerase-chain-reaction (PCR) assay. The analysis included all data collected up to April 27, 2017, the date of the last delivery in the cohort.

RESULTS

Among the 555 fetuses and infants in the 546 pregnancies included in the analysis, 28 (5.0%) were not carried to term or were stillborn, and 527 were born alive. Neurologic and ocular defects possibly associated with ZIKV infection were seen in 39 fetuses and infants (7.0%; 95% confidence interval, 5.0 to 9.5); of these, 10 were not carried to term because of termination of pregnancy for medical reasons, 1 was stillborn, and 28 were live-born. Microcephaly (defined as head circumference more than 2 SD below the mean for sex and gestational age) was detected in 32 fetuses and infants (5.8%), of whom 9 (1.6%) had severe microcephaly (more than 3 SD below the mean). Neurologic and ocular defects were more common when ZIKV infection occurred during the first trimester (24 of 189 fetuses and infants [12.7%]) than when it occurred during the second trimester (9 of 252 [3.6%]) or third trimester (6 of 114 [5.3%]) (P=0.001).

CONCLUSIONS

Among pregnant women with symptomatic, PCR-confirmed ZIKV infection, birth defects possibly associated with ZIKV infection were present in 7% of fetuses and infants. Defects occurred more frequently in fetuses and infants whose mothers had been infected early in pregnancy. Longer-term follow-up of infants is required to assess any manifestations not detected at birth. (Funded by the French Ministry of Health and others; ClinicalTrials.gov number, NCT02916732.)

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A Quick Take is available at NEJM.org

It has been recognized recently that Zika virus (ZIKV) infection during pregnancy can cause severe birth defects,[1] including microcephaly,[2] other brain defects,[3] and the congenital Zika syndrome.[4] However, the magnitude of this risk is not clearly defined. It was estimated to be higher than 40% in a prospective observational study in Brazil involving women who had symptomatic ZIKV infection during pregnancy.[3] In the U.S. Zika Pregnancy Registry, the estimate was 6% overall and 11% when ZIKV exposure occurred during the first trimester.[5] The latter estimate has been updated recently to 15%.[6]

The ZIKV epidemic in French territories in the Americas began in early 2016 and presented another opportunity to assess the risk of ZIKV-related congenital neurologic defects in a population of pregnant women living in a region in which a ZIKV outbreak occurred. The centralized antenatal and maternal care facilities enabled enhanced surveillance of all pregnancies during the ZIKV epidemic. We present here the pregnancy outcomes in a cohort of women living in French territories in the Americas (French Guiana, Guadeloupe, and Martinique) who had symptomatic, laboratory-confirmed ZIKV infection during pregnancy.

Methods

Study Overview

ZIKA-DFA-FE was a cohort study that used four different recruitment methods in an attempt to capture all women whose pregnancies overlapped with the period of the ZIKV epidemic in French territories in the Americas (details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The study received ethics approval from Comité de Protection des Personnes Sud-Ouest et Outre Mer III. All participants provided written informed consent. Full details of the study design can be found in the protocol, available at NEJM.org. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. The study protocol was prepared with the help of the INSERM Research and Action Targeting Emerging Infectious Disease (REACTing) network.

A key component of the ZIKA-DFA-FE study was the prospective follow-up, until the end of pregnancy, of women who had clinical symptoms of ZIKV infection during pregnancy. In accordance with the guidelines of the French High Council for Public Health[7] and the French National College of Gynecologists and Obstetricians[8] that were released on July 28, 2015, and February 5, 2016, respectively, whenever a pregnant woman presented to the outpatient clinic or emergency department of a participating center with symptoms consistent with acute ZIKV infection, she underwent a clinical examination, and blood and urine specimens were obtained for confirmation of recent ZIKV infection.

Enrollment Criteria

Pregnant women with suspected ZIKV infection were referred to the prenatal diagnosis center in each territory, where they underwent testing for ZIKV infection and were invited to participate in the study. Women were included in this analysis if they met all of the following criteria: ongoing pregnancy at any gestational stage; clinical symptoms consistent with acute ZIKV infection, with at least one symptom of pruritic skin rash, fever, conjunctival hyperemia, arthralgia, or myalgia; and laboratory confirmation of recent ZIKV infection, on the basis of a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay performed on a specimen of blood, urine, or both. The date of ZIKV infection was considered to be the date of the first ZIKV-related symptom onset.

Cohort Follow-up and End Points

Once women were enrolled, they underwent monthly clinical and ultrasonographic examinations until they had a pregnancy outcome. During these follow-up visits, a clinician also inquired about events that may have occurred (e.g., pregnancy complications or treatments received) since the previous visit. If a fetal abnormality was identified during a follow-up ultrasonographic examination, magnetic resonance imaging (MRI) of the fetus was performed, and the woman was followed up monthly with laboratory testing and ultrasonography, as reported elsewhere.[9-11] The end point for each woman enrolled in the study was the pregnancy outcome: delivery of a live-born infant with or without birth defects, miscarriage, termination of pregnancy for medical reasons, or stillbirth.

DATA AND SAMPLE COLLECTION IN MOTHERS

During the enrollment visit, sociodemographic data were collected for each woman. These data included age, ethnic group, residence, level of education, professional activity, and lifestyle factors. Clinical information — including the number of previous pregnancies and live births, history of adverse pregnancy outcomes, pertinent medical history, body-mass index, symptoms of ZIKV infection, gestational age of fetuses, and any clinically relevant medical event during pregnancy — was recorded during this baseline visit, and blood and urine specimens were obtained.

Laboratory tests included RT-PCR for the detection of ZIKV (RealStar Zika Virus RT-PCR Kit 1.0, Altona Diagnostics) in blood, urine, or both at baseline in all women and at the end of pregnancy in the case of fetal death, termination of pregnancy, or stillbirth. In addition, results of TORCH serologic testing[12,13] (toxoplasmosis, other [syphilis, varicella, parvovirus infection, human immunodeficiency virus infection], rubella, cytomegalovirus infection, and herpes simplex virus infection), which is routinely performed during pregnancy in French territories in the Americas, were recorded. Serologic testing for cytomegalovirus was performed only on an elective basis, when fetal abnormalities were detected.

DATA COLLECTION IN INFANTS

For live-born infants, maternal and cord-blood specimens were obtained on the day of delivery, and serum specimens were frozen. The following information on these infants was also recorded on the day of birth: gestational age, length, weight, head circumference, Apgar score at 5 minutes of life, and the results of a standardized clinical examination.

PREGNANCY OUTCOMES

Pregnancy outcomes included delivery of a live-born child (with or without abnormalities) or pregnancy loss through miscarriage, termination of pregnancy, or stillbirth. For the purpose of comparison with other studies,[5] miscarriage was defined as intrauterine fetal death that occurred before a gestational age of 20 weeks. Stillbirth was defined as intrauterine fetal death that occurred at or after a gestational age of 20 weeks or intrapartum death during delivery.

Likewise, to allow for comparison with other studies, we summarized our data in two mutually exclusive categories: birth defects possibly associated with ZIKV infection[5] (brain abnormalities with or without microcephaly regardless of the presence of additional birth defects); and neural-tube defects and other early brain malformations (e.g., anencephaly, acrania, encephalocele, holoprosencephaly, or arhinencephaly), eye abnormalities, and other consequences of central nervous system dysfunction among fetuses and infants who had neither evident brain abnormalities nor microcephaly. Consequences of central nervous system dysfunction included conditions such as arthrogryposis, clubfoot, congenital hip dysplasia, and congenital deafness. In the case of live birth, microcephaly was defined as moderate when the head circumference was between 3 SD and 2 SD below the mean and severe when the head circumference was more than 3 SD below the mean, on the basis of INTERGROWTH-21st standards (http://intergrowth21.ndog.ox.ac.uk/) for sex and gestational age. Moderate microcephaly was further defined as proportionate or disproportionate — proportionate if the neonate was small for gestational age and disproportionate if the neonate was not small for gestational age.[14] Small for gestational age was defined as a weight more than 1.28 SD below the mean according to the INTERGROWTH-21st standards for sex and gestational age. In the case of pregnancy loss or termination of pregnancy for medical reasons, autopsy measurements when available and findings from the last ultrasonographic examination were used to assess for microcephaly. When ultrasonographic findings were used instead of autopsy data, microcephaly was defined as a head circumference more than 3 SD below the mean.

In addition, we specified the number of fetuses and infants who had any of the severe neurologic birth defects that are included in the currently proposed definition of the congenital Zika syndrome: severe microcephaly (head circumference more than 3 SD below the mean), brain abnormalities with a specific pattern of damage (e.g., calcifications, ventriculomegaly, or cortical malformations), damage to the back of the eye, joints with limited range of motion (e.g., clubfoot), or hypertonia that restricts body movement (e.g., arthrogryposis).[4]

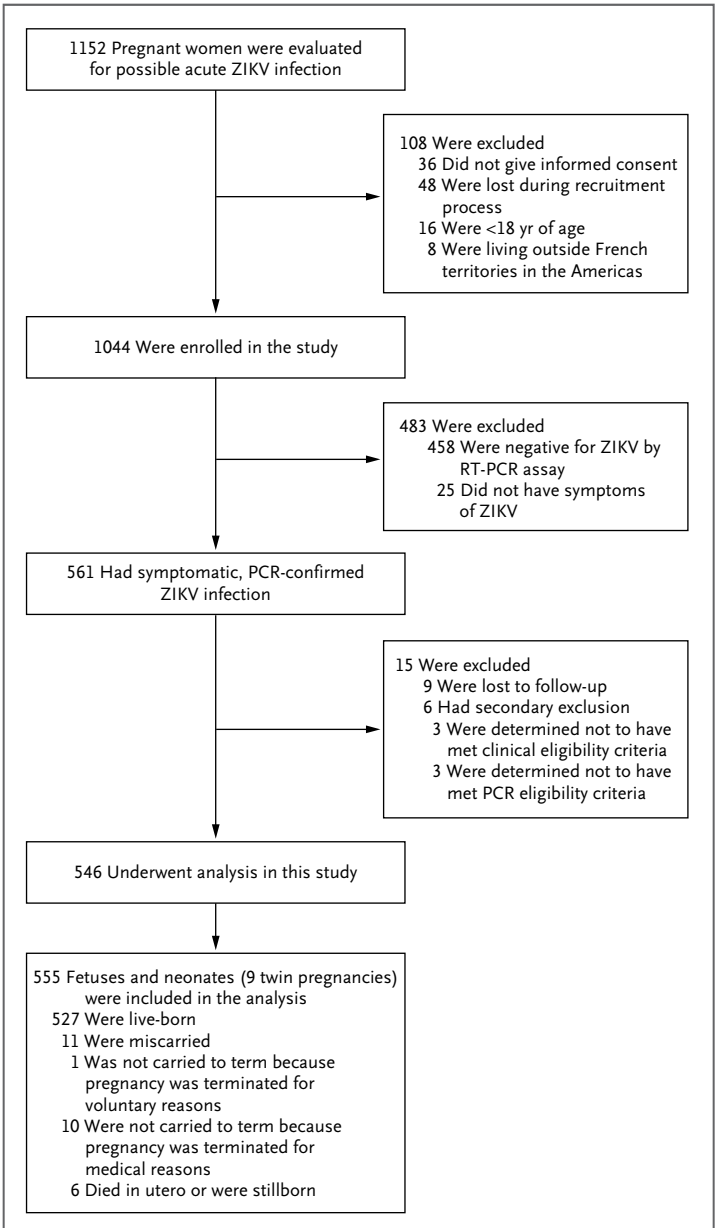

Figure 1. Prospective Maternal Cohort and Pregnancy Outcomes.

The study was performed in the French territories of Martinique, Guadeloupe, and French Guiana. PCR denotes polymerase chain reaction, RT-PCR, reverse-transcriptase–PCR, and ZIKV Zika virus.

STATISTICAL ANALYSIS

The analysis included all data collected up to April 27, 2017, the date of the last delivery in the cohort. The percentage of fetuses and infants with birth defects possibly associated with ZIKV infection was estimated according to the trimester in which pregnant women were infected, and we compared these values across the three groups using Fisher's exact test. Data were analyzed with the use of Stata software, version 13 (StataCorp).

RESULTS

PATIENTS

From March 2, 2016, to November 24, 2016, a total of 1152 pregnant women were evaluated at prenatal diagnosis centers for possible acute ZIKV infection. Of these, 108 were not enrolled in the study because they declined to participate (36 women), were lost to follow-up during the recruitment process (48), were younger than 18 years of age (16), or were living outside French territories in the Americas (8); 458 had a negative result on ZIKV RT-PCR; and 25 had none of the qualifying symptoms. Thus, 561 women with symptomatic, PCR-confirmed, ZIKV infection were included in the analysis in this study. Of these, 6 women (1.1%) were excluded after it was determined that they did not meet specific eligibility criteria regarding clinical or PCR results, and 9 women (1.6%) were lost to follow-up. Among these 9 women, the last available ultrasonographic data were from the third trimester for 5 women and from the second trimester for 4 women; these fetal ultrasonographic examinations were normal. Among the 546 women whose pregnancy outcome was known, there were 9 twin pregnancies. We were therefore able to describe outcomes in 555 fetuses and infants (Fig. 1). The 9 twin pregnancies resulted in 17 live births and 1 miscarried fetus. No abnormalities were detected in any of the live-born infants from twin pregnancies. In the twin pregnancy that resulted in 1 live birth and 1 miscarried fetus, the mother had been infected with ZIKV during the sixth week of pregnancy; the loss of 1 fetus occurred at 10 weeks of gestation, and the other fetus was carried to 41 weeks of gestation and was born healthy, without any abnormalities. Table 1 shows the main characteristics of the 546 women (mean age, 29.7 years) with known pregnancy outcomes, and Table 2 shows the main characteristics of ZIKV infection in these women. Coinfections with TORCH microorganisms are shown in Table 3.

PREGNANCY OUTCOMES

Pregnancy outcomes are shown in Table 4 and in Table S2 in the Supplementary Appendix. Of the 546 women with known outcomes, 185 (33.9%) were infected with ZIKV in the first trimester of

pregnancy, 249 (45.6%) in the second trimester, and 112 (20.5%) in the third trimester. Overall, the mean number of fetal ultrasonographic examinations performed between the date of ZIKV infection and pregnancy outcome was 3.5 when ZIKV infection occurred during the first trimester and 2.2 when it occurred during the second trimester. A total of 28 fetuses (5.0%) were not carried to term or were stillborn; there were 11 miscarriages, 10 terminations of pregnancy for medical reasons, 6 stillbirths, and 1 voluntary abortion. Among the 527 live births, 69 infants (13.1%) were small for gestational age, and 75 infants (14.2%) were delivered through emergency cesarean section. A total of 31 infants (5.9%) were hospitalized immediately after birth, and 7 of these infants (1.3%) were admitted to the neonatal intensive care unit. A total of 8 infants (1.5%) had an Apgar score of less than 7 at 5 minutes after birth. These percentages did not differ by trimester of infection.

Neurologic and ocular abnormalities possibly associated with ZIKV infection were observed in 39 fetuses and infants (7.0%; 95% confidence interval [CI], 5.0 to 9.5): 28 live-born infants, 10 fetuses that were not carried to term because of termination of pregnancy for medical reasons, and 1 stillborn baby. Microcephaly was detected in 32 fetuses and infants (5.8%): 9 cases (1.6%) were severe, 9 (1.6%) were moderate-disproportionate, and 14 (2.5%) were moderate-proportionate. Additional defects were observed in only 1 of the 23 infants with moderate microcephaly — a case involving medical termination of pregnancy in which the fetus had moderate-disproportionate microcephaly. Severe microcephaly or other brain abnormalities included in the current definition of the congenital Zika syndrome were seen in 17 fetuses and infants (3.1%). In 3 of the 527 live births (0.6%), clinical abnormalities other than microcephaly were detected at birth. Neurologic and ocular abnormalities were more common when ZIKV infection had occurred during the first trimester (24 of 189 fetuses and infants [12.7%]) than when it had occurred during the second trimester (9 of 252 [3.6%]) or third trimester (6 of 114 [5.3%]) (P=0.001). The same was true for severe microcephaly (3.7%, 0.8%, and 0.0%, respectively; P=0.02) and the congenital Zika syndrome (6.9%, 1.2%, and 0.9%, respectively; P=0.002). The risk of birth defects possibly associated with ZIKV infection was similar in Guadeloupe and Martinique (7.2% and 7.5%, respectively). The risk of birth defects included in the current definition of the congenital Zika syndrome was also similar in the two terri-

Table 1. Characteristics of the Women with Symptomatic, PCR-Confirmed ZIKV Infection.*

Characteristic	Study Cohort (N=546)
Residence — no. (%)	
French Guiana	24 (4.4)
Guadeloupe	245 (44.9)
Martinique	277 (50.7)
Age — yr	
Mean	29.7±6.2
Range	18–46
Occupation — no. (%)	
Student	23 (4.2)
Artisan, merchant, or business owner	30 (5.5)
Professional	111 (20.3)
Employee	177 (32.4)
Laborer, factory worker, or farmer	5 (0.9)
Unemployed	187 (34.2)
Missing data or declined to respond	13 (2.4)
Medical history — no. (%)	
Arterial hypertension	23 (4.2)
Diabetes	8 (1.5)
Sickle cell disease	4 (0.7)
Previous pregnancies — no. (%)	
0	131 (24.0)
1	153 (28.0)
2	126 (23.1)
≥3	136 (24.9)
Previous adverse pregnancy outcomes — no. (%)	
Congenital abnormalities	6 (1.1)
Stillbirth	10 (1.8)
Termination of pregnancy for medical reasons	10 (1.8)
Mean BMI before pregnancy†	26.1±6.3
Lifestyle practices during this pregnancy — no. (%)	
Alcohol consumption	2 (0.4)
Drug use	6 (1.1)
Current smoker	23 (4.2)
Use of mosquito repellents	445 (81.5)
Use of larvicides	337 (61.7)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. PCR denotes polymerase chain reaction, and ZIKV Zika virus.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Data on BMI are missing for 90 women (16.5%).

Table 2. Characteristics of Infection in the Women with Symptomatic, PCR-Confirmed ZIKV Infection.

Characteristic	Study Cohort (N = 546)
	no. (%)
Trimester of symptomatic ZIKV infection	
First	185 (33.9)
Second	249 (45.6)
Third	112 (20.5)
Number of symptoms at time of ZIKV diagnosis	
1	66 (12.1)
2	111 (20.3)
3	121 (22.2)
4	95 (17.4)
≥5	153 (28.0)
ZIKV symptoms	
Rash	519 (95.1)
Arthralgia	300 (54.9)
Itching	263 (48.2)
Conjunctival hyperemia	199 (36.4)
Headache	161 (29.5)
Myalgia	128 (23.4)
Fever	123 (22.5)
Limb swelling	104 (19.0)
Pain behind eyes	102 (18.7)
Petechiae	38 (7.0)
Bleeding	1 (0.2)

tories (3.6% and 2.8%, respectively). In French Guiana, where the number of participants (24) was small, no birth defects possibly associated with ZIKV infection were observed. There was no significant association between any potentially identifiable toxic prenatal exposures (i.e., larvicides, repellants, alcohol, tobacco, or illicit drugs) and birth defects.

No fetal abnormality or birth defect was observed in any of the women who had coinfection with syphilis (4 women), human immunodeficiency virus (2), toxoplasmosis (3), or cytomegalovirus (1). A total of 31 women underwent amniocentesis during the course of their pregnancy, with 27 instances of karyotyping and 20 ZIKV RT-PCR assays. All karyotypes were normal except for one pericentric inversion of chromosome 2, and RT-PCR for ZIKV in an amniotic-fluid specimen was positive in 7 cases. In addition, 6 nonneurologic birth defects (in 1.1% of the fetuses or infants) were detected in this cohort (see Table S3 in the Supplementary Appendix for a detailed description of all birth defects).

DISCUSSION

The main findings of this cohort study are twofold. First, we found a 7.0% overall risk of neurologic and ocular defects possibly associated with ZIKV infection that were evident at birth in the offspring of women in French territories in the Americas who had acute, symptomatic, PCR-confirmed ZIKV infection during pregnancy. The overall risk of evident birth defects included in the current definition of the congenital Zika syndrome was 3.1%, and the overall risk of severe microcephaly was 1.6%. Second, although birth defects could be observed as a consequence of ZIKV infection in any trimester of pregnancy, our data showed that the risk of birth defects and the risk of the congenital Zika syndrome were higher when ZIKV infection occurred early in pregnancy — a finding consistent with previous reports.[5,15] The risk of birth defects was 12.7% when ZIKV infection occurred in the first trimester, 3.6% when it occurred in the second trimester, and 5.3% when it occurred in the third trimester, and the risk of the congenital Zika syndrome was 6.9%, 1.2%, and 0.9%, respectively.

The percentage of fetuses and infants with neurologic birth defects (7%) in this study is similar to the 6% observed in the cohort of women in the United States[5] and the 5% reported more recently in the U.S. territories,[15] but it is much lower than the 42% observed in the Brazilian cohort.[3] The difference is not attributable to the percentage of infants and fetuses with microcephaly — which is similar in the current study in French territories in the Americas, in the study in the United States, and in the study in Brazil (5.8%, 4.1%, and 3.4%, respectively) — but rather to the percentage with wider neurologic birth defects. The percentage of infants who were small for gestational age was similar in French territories in the Americas and in the Brazilian cohort (13.1% and 9%, respectively), but differences between those two cohorts are apparent when we examine the percentage of infants who were admitted to neonatal intensive

Table 3. Results of ZIKV and TORCH Testing in the 546 Women with Symptomatic, PCR-Confirmed ZIKV Infection.*

Test	Time of ZIKV Infection		
	First Trimester	Second Trimester	Third Trimester
		no. of women (%)	
ZIKV RT-PCR			
Positive results	185 (100.0)	249 (100.0)	112 (100.0)
In blood and urine	121 (65.4)	159 (63.9)	66 (58.9)
In blood only†	40 (21.6)	63 (25.3)	23 (20.5)
In urine only‡	24 (13.0)	27 (10.8)	23 (20.5)
TORCH§			
Positive results on any TORCH test	6 (3.2)	2 (0.8)	2 (1.8)
Toxoplasmosis¶			
Tested	165 (89.2)	235 (94.4)	105 (93.8)
Positive	1 (0.6)	0	2 (1.9)
Syphilis			
Tested	150 (81.1)	206 (82.7)	87 (77.7)
Positive	4 (2.7)	0	0
HIV			
Tested	161 (87.0)	210 (84.3)	97 (86.6)
Positive	1 (0.5)	1 (0.4)	0
Rubella¶			
Tested	152 (82.2)	222 (89.2)	97 (86.6)
Positive	0	0	0
Cytomegalovirus¶			
Tested	20 (10.8)	30 (12.0)	14 (12.5)
Positive	0	1 (3.3)	0

* TORCH includes testing for toxoplasmosis, other (syphilis, varicella, parvovirus infection, human immunodeficiency virus infection), rubella, cytomegalovirus infection, and herpes simplex virus infection. In highly febrile women, a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for dengue virus was performed on blood specimens. Of the 267 tests performed, 1 was positive. HIV denotes human immunodeficiency virus.
† Results from tests on urine specimens were negative or unknown, or tests were not performed.
‡ Results from tests on blood specimens were negative or unknown, or tests were not performed.
§ In the subcategories of TORCH, the denominators for the percent of women who tested positive are the numbers of women tested.
¶ Toxoplasmosis, rubella, and cytomegalovirus tests were for IgM antibodies.

care immediately after birth (1.3% in the French territories and 21% in Brazil) and the percentage of infants with abnormal neurologic findings from the clinical examination at birth (0.6% and 26.5%, respectively). The termination of 10 pregnancies for medical reasons in the French territories (as compared with none in Brazil) may have resulted in fewer neurologic abnormalities being detected at birth in the French territories than in Brazil, but this cannot explain the entire difference between the two cohorts. In addition, the extensive use of MRI in the Brazilian cohort may have resulted in isolated abnormal imaging findings that have not been observed in other studies in which the use of MRI has been less frequent. The clinical implications of these findings in Brazil are not yet known and will be determined only through longer-term follow-up of infants.

The strengths of our study include the size and homogeneity of the cohort of pregnant women who were living in a region in which an outbreak

Table 4. Birth Outcomes and Abnormalities Observed in the Fetuses and Infants.*

Variable	Time of ZIKV Infection			
	First Trimester (N=189)	Second Trimester (N=252)	Third Trimester (N=114)	Total (N=555)
	no. of fetuses or infants (%)			
Birth outcome				
Stillborn or not carried to term	24 (12.7)	4 (1.6)	0	28 (5.0)
Miscarried	11 (5.8)	0	0	11 (2.0)
Not carried to term because of voluntary termination of pregnancy	1 (0.5)	0	0	1 (0.2)
Not carried to term because of termination of pregnancy for medical reasons	9 (4.8)	1 (0.4)	0	10 (1.8)
Stillborn	3 (1.6)	3 (1.2)	0	6 (1.1)
Live-born	165 (87.3)	248 (98.4)	114 (100)	527 (95.0)
No prenatal ultrasonography after ZIKV infection†	13 (6.9)	28 (11.1)	55 (48.2)	96 (17.3)
Abnormalities observed				
Neurologic or ocular birth defects‡	24 (12.7)	9 (3.6)§	6 (5.3)	39 (7.0)
Microcephaly¶	19 (10.1)	8 (3.2)	5 (4.4)	32 (5.8)
Severe	7 (3.7)	2 (0.8)	0	9 (1.6)
Moderate: disproportionate	4 (2.1)	2 (0.8)	3 (2.6)	9 (1.6)
Moderate: proportionate	8 (4.2)	4 (1.6)	2 (1.8)	14 (2.5)
Intracranial calcifications	8 (4.2)	0	0	8 (1.4)
Ventriculomegaly	7 (3.7)	1 (0.4)	0	8 (1.4)
Lissencephaly	2 (1.1)	0	0	2 (0.4)
Other brain abnormalities	8 (4.2)	1 (0.4)	0	9 (1.6)
Neural-tube defects	1 (0.5)	0	0	1 (0.2)
Eye abnormalities	0	0	0	0
Consequences of central nervous system dysfunction	1 (0.5)	0	1 (0.9)	2 (0.4)
Other birth defects	2 (1.1)	3 (1.2)	1 (0.9)	6 (1.1)
Chromosomal defects	0	1 (0.4)‖	0	1 (0.2)
Skeletal abnormalities	2 (1.1)	1 (0.4)	1 (0.9)	4 (0.7)
Other	0	1 (0.4)	0	1 (0.2)
Congenital Zika syndrome	13 (6.9)	3 (1.2)	1 (0.9)	17 (3.1)

* A total of 546 pregnancies were included in the study; there were 9 twin pregnancies, which brought the total number of fetuses and infants to 555.

† Among the 527 live births, 96 infants (18.2%) did not undergo prenatal ultrasonography after the mother had been infected with ZIKV (7.9% when ZIKV infection occurred in the first trimester, 11.3% when infection occurred in the second trimester, and 48.3% when infection occurred in the third trimester).

‡ These results are possibly associated with ZIKV infection. Fetuses or infants may have had more than one neurologic or ocular defect.

§ The mother of one of these infants also had parvovirus B19 infection.

¶ In the case of live birth, microcephaly was defined as a head circumference more than 2 SD below the mean, on the basis of INTERGROWTH-21st standards (http://intergrowth21.ndog.ox.ac.uk/) for sex and gestational age. Microcephaly was considered moderate when the head circumference was between 3 SD and 2 SD below the mean and severe when the head circumference was more than 3 SD below the mean. Moderate microcephaly was further defined as proportionate or disproportionate — proportionate if the neonate was small for gestational age (a weight more than 1.28 SD below the mean for sex and gestational age) and disproportionate if the neonate was not small for gestational age. In the case of pregnancy loss or termination of pregnancy for medical reasons, autopsy measurements when available and findings from the last ultrasonographic examination were used to assess for microcephaly. When ultrasonographic findings were used instead of autopsy data, microcephaly was defined as a head circumference more than 3 SD below the mean.

‖ This infant had Down's syndrome with severe microcephaly.

of ZIKV occurred and who were prospectively followed from the time that acute symptoms developed and ZIKV infection was confirmed by PCR until the pregnancy outcome. The diagnosis of ZIKV infection was made on the basis of PCR testing of specimens of blood or urine or both, and the date of infection could be ascertained because the date of symptom onset was close to the date of ZIKV PCR testing. The study was conducted in well-defined geographic areas, and high standards of care were available to all pregnant women living in these territories. Linkage to care of pregnant women with ZIKV infection was effective, with a low rate of loss to follow-up (1.6%). In addition, the results were consistent across the two territories in which the largest numbers of women were recruited (Martinique and Guadeloupe).

We acknowledge that our study has limitations. First, it focused only on pregnant women who had acute, symptomatic ZIKV infection. Although the rate of complications would be expected to be higher among women with symptomatic infection than among those who were asymptomatic, an observational study involving U.S. women did not show any significant difference in the rate of birth defects between the offspring of women who had symptomatic ZIKV infection and the offspring of women who had asymptomatic ZIKV infection during pregnancy.[5] A recent study also showed no significant association between disease severity or viral load and adverse outcomes.[16] Second, we were not able to fully assess the presence of birth defects possibly associated with ZIKV infection in the case of the 11 miscarriages, 2 of the 6 stillbirths, and the 1 voluntary abortion, as well as in the 96 live-born infants (18.2% of the 527 live-born infants) who did not undergo prenatal ultrasonography after ZIKV infection. Although missing ultrasonographic data may have led to underdiagnosis of ZIKV-related birth defects, it should be noted that in our cohort, only 1 live-born baby had an isolated brain abnormality (ventriculomegaly), detected by MRI, in the absence of clinical abnormalities, after infection during the second trimester of pregnancy. All other live-born babies with ZIKV-related defects had at least one abnormality that would have been detected during the clinical examination at birth (e.g., microcephaly, clubfoot, or a neural-tube defect such as spina bifida). Also, the majority of missing ultrasonographic data involved pregnancies in which infection occurred during the third trimester, and the consequences of infection during the third trimester were found to be limited in the other infants of the same cohort. Third, our end point was based on fetal ultrasonography and on neonatal clinical examinations and did not include postnatal ultrasonography or specialized hearing and ophthalmologic examinations. We believe that this aspect of the study design had a limited effect on the rate of birth defects that could have been identified if all neonates had undergone brain imaging soon after birth. Indeed, it has been reported that when ZIKV infection occurs during the first trimester or early second trimester, all brain abnormalities can be detected with ultrasonography before 28 weeks of gestation.[10] Another study showed that none of 103 infants with normal prenatal ultrasonographic findings and normal clinical examinations at birth had anomalies attributable to ZIKV when MRI of the head was performed after birth.[17] Still, the absence of microcephaly at birth does not exclude the possibility of delayed development of microcephaly or other ZIKV-related brain and other abnormalities.[18] This information is now being collected as part of a cohort study of the infants (ClinicalTrials.gov number, NCT02810210); the study includes regular clinical examinations with specialized hearing and ophthalmologic testing. Only the longer-term follow-up of the children born to the women in the current study will help identify the full spectrum of ZIKV-related complications.

In conclusion, among pregnant women with PCR-confirmed, symptomatic ZIKV infection, birth defects possibly associated with ZIKV infection were present in 7% of fetuses and infants. Defects were more common among fetuses and infants whose mothers had been infected early in pregnancy. Longer-term follow-up of infants is required to assess for late-onset manifestations not detected at birth.

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APPENDIX

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