



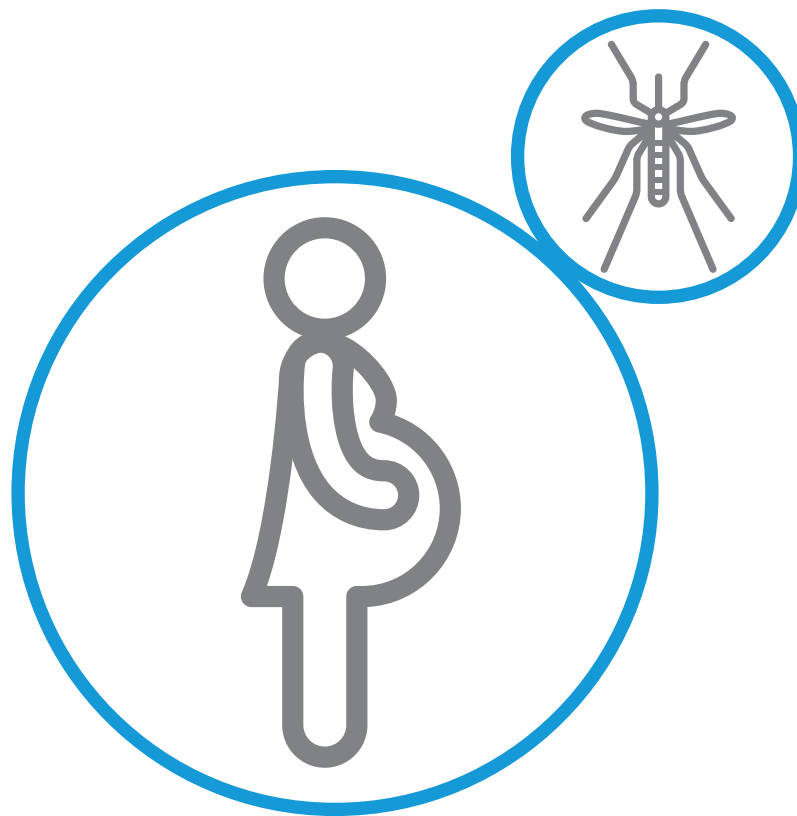
Provisional considerations for the care of pregnant women in settings with high Zika virus circulation: document for health care professionals



Pan American
Health
Organization



World Health
Organization
REGIONAL OFFICE FOR THE
Americas



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May 2, 2016



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This document was developed by PAHO/WHO based on antenatal care recommendations, together with the data and evidence currently available on the impact of the Zika virus on pregnant women. These considerations will be revised and updated as new evidence becomes available.

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I. INTRODUCTION

The Zika virus is a flavivirus transmitted by mosquitoes that belong to the *Aedes* genus. It was first isolated in 1947 in Rhesus macaques of the Zika Forest (Uganda); human infection was initially shown through serology studies in Uganda and Tanzania in 1952, and the virus was successfully isolated from human samples in Nigeria in 1968 ⁽¹⁾.

The first autochthonous case in the Americas was reported in February 2014 by the Ministry of Health of Chile (Easter Island) ⁽²⁾. However, since February 2015 the number of cases reported by the Ministry of Health of Brazil has soared ⁽³⁾. In October 2015 the ministry warned about an unusual increase in the number of cases of microcephaly reported in the State of Pernambuco, where 141 cases were reported in less than one year, versus only about 10 reported cases in past years ⁽⁴⁾. Further investigations confirmed the presence of the Zika virus genome through the real-time polymerase chain reaction (RT-PCR) technique applied to the amniotic fluid of two pregnant women in Paraíba, whose fetuses presented microcephaly as reported in their prenatal ultrasonography scans ⁽⁵⁾. Also in Brazil, in November 2015, the presence of the Zika virus genome was verified in tissue specimens and blood samples of a dead newborn with microcephaly ⁽⁶⁾. These findings have been confirmed through immunohistochemistry by the CDC, as reported by Brazil in early January 2016 ⁽⁷⁾. A study by Fiocruz-Paraná using histochemistry confirmed the presence of the virus in the placenta ⁽⁸⁾. Since similar situations were reported by other local governments, the Ministry of Health of Brazil declared a national public health emergency ⁽⁹⁾.

Based on the various findings, since May 7, 2015, the Pan American Health Organization has issued a number of epidemiological alerts (May, November, and December 2015) ^(1, 6, 10) and two epidemiological updates (October 2015 and January 2016) ^(11, 12). Relevant information on the topic has also been brought together at a Web site specifically dedicated to the issue, www.paho.org/viruszika.

As of April 28, 2016, 35 countries and territories have confirmed autochthonous circulation of Zika virus in the Americas: Aruba, Barbados, Belize, Bolivia, Bonaire, Brazil, Colombia, Costa Rica, Cuba, Curaçao, Dominica, Ecuador, El

Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Saint Lucia, Saint Martin, Sint Maarten, Suriname, Trinidad and Tobago, the U.S. Virgin Islands, and Venezuela, www.paho.org/viruszika.

On February 1, 2016, the Emergency Committee, convened by the Director of WHO in response to the increase in microcephaly and other neurological defects in Brazil, declared a public health emergency of international concern.

Given the introduction of this new virus in the Americas and its potential association with microcephaly and other fetal anomalies, this document presents provisional considerations on Zika virus infection in pregnant women. These considerations are based on four overarching principles, as follows:

- Health care providers, administrators, and policymakers should ensure that the sexual and reproductive rights of pregnant women are protected during the delivery of information and services related to Zika virus infection.
- The privacy of pregnant women infected with Zika virus should be respected during care, which includes ensuring the confidentiality of information by medical and other personnel.
- Education and provision of services should be based on accurate, up-to-date scientific information, so as to discourage harmful practices.
- Access to information and comprehensive services should be provided to all pregnant women, voluntarily, without discrimination or coercion, and respecting individual choices.



II. AIM / OBJECTIVES OF THE DOCUMENT

The aim of this document is to provide health care professionals in charge of the care of pregnant women with updated information based on the best evidence available for the prevention of infection, timely diagnosis, suggested symptomatic therapy and monitoring of pregnant women, and notification of cases to the competent health authorities.

The information presented in this document was updated on April 28, 2016; it may be further altered if new evidence appears on the effects / consequences of Zika virus infection in pregnant women and their children. New updates may also be found regularly at www.paho.org/viruszika.

III. PREVENTION OF ZIKA VIRUS INFECTION

Prevention of infection in pregnant women is exactly the same as that recommended for the general population. Health care professionals should promote the following measures, both in the community and with pregnant women and their families.

- i. Environmental measures** are collective and are aimed at reducing vector density. Mosquito control is the main measure that can successfully interrupt transmission of viruses such as dengue, Zika and chikungunya.

This information is further developed in PAHO's epidemiological alert issued on May 7, 2015 under the heading of Zika Virus Infection ⁽⁶⁾.

More than 90% of mosquito breeding sites are inside and around dwellings. As a result, it is essential to reduce the mosquito population and the best way to do this is to eliminate their breeding sites. **This is the most effective action.** The control of mosquito breeding sites inside and around dwellings, and in public and/or private places, should be everyone's responsibility --authorities, public sector, private sector, NGOs, families, and individuals--, not just the health sector's.

In order to eliminate mosquitoes, weekly tasks should be recommended to **prevent water build-up in containers outside and around dwellings (in flower pots, bottles, and containers where water can accumulate); cover domestic water tanks; avoid accumulating garbage (deposit it in closed plastic bags and use closed containers); and unblock drains to prevent stagnant water.**

- ii. Personal protection measures:** These measures complement the main one: the elimination of breeding sites. People should wear clothing that minimizes skin exposure (trousers and long sleeves), and should use protective screens in doors and windows. They can also use repellents authorized for human use, such those containing DEET (N, N-Diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester) or icaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester), which can be applied to exposed skin or clothes, and should be **used in strict accordance with the instructions on the product label.** There is no evidence to restrict use of these repellents by pregnant women provided that they use them according to the instructions on the product label. It is important to tell people that these measures should always be taken together with breeding site elimination activities, thereby increasing their effectiveness.
- iii. Patient isolation.** This measure is intended to prevent infected people, during the first week of the disease (viremic phase), from being bitten by uninfected mosquitoes that could become new transmitters of the disease ⁽⁶⁾.



IV. ZIKA VIRUS INFECTION DURING PREGNANCY

- i. Clinical issues:** No clinical differences have been described between pregnant and non-pregnant women. After an infected mosquito bite, symptoms of the disease typically appear after a three- to twelve-day incubation period. Infection may progress asymptotically in a substantial portion of cases (70-80%), or present with the following clinical features ⁽⁶⁾:

Table 1. Symptoms of Zika virus infection

Core symptoms of Zika virus infection	
Fever 37.2°C to 38°C	Muscle and/or joint pain
Itchy maculopapular rash	Weakness
Non-purulent conjunctivitis	Edema of the lower limbs
Headache	
Less common symptoms	
Retro-orbital pain	Anorexia
Vomiting, diarrhea	Abdominal pain

Symptoms last 4-7 days, and are usually self-limited ⁽¹⁾.

In the context of Zika virus circulation, several countries in the Region have reported an increased occurrence of neurological syndromes, including, but not limited to Guillain-Barré Syndrome (GBS), meningoencephalitis, and myelitis. Although a causal relation with Zika virus has not yet been established, there is a high degree of suspicion that these manifestations are caused by the virus ⁽⁶⁾.

- ii. Diagnosis:** The diagnostic steps recommended for pregnant women are exactly the same as those recommended for the general population, and they are defined in PAHO's epidemiological update released on October 16, 2015 ⁽¹⁴⁾.

ii a. **Clinical diagnosis:**

Based on clinical suspicion, namely, onset of one or several of the above-described symptoms in a pregnant woman living in or who has recently been in an area where circulation of the virus has been verified. Infection may also be suspected if symptoms develop in women whose sexual partners had recently been in areas where viral transmission is occurring ⁽¹⁵⁾.

ii b. **Differential clinical diagnosis:**

Established with other infections causing rash and fever, particularly those caused by flaviviruses such as dengue, chikungunya or West Nile, among others.

ii c. **Diagnostic confirmation:**

Confirmation requires a local or reference laboratory capable of performing the tests described below. The team in charge of the pregnant woman's care must contact the appropriate health authority to determine the type of samples that need to be taken.

ii c1. **Virological diagnosis:**

Consists of identifying the viral nucleic acid through a reverse transcription polymerase chain reaction (RT-PCR) test. The type of specimens required may depend on the days elapsed since the onset of symptoms. Viral RNA may be found in serum up to about 5 days after the onset of symptoms; in urine it may be identified a few days more ⁽¹⁴⁾. Furthermore, viral RNA may be found in saliva or urine specimens collected during the first 3-5 days following the onset of symptoms ⁽¹⁶⁾. If viral RNA has been detected in the amniotic fluid, under exceptional situations or in research protocols, amniotic fluid samples could also be used. Isolation of the virus is more complex, and is usually restricted to research settings ⁽¹⁴⁾.

ii c2. **Serological diagnosis:**

Zika virus anti-IgM antibodies are detected through ELISA or immunofluorescence, no earlier than the fifth day after onset of symptoms. The interpretation of serological assays is particularly relevant for the diagnosis of Zika virus. In primary infections (first infection with a flavivirus) cross reactions with other genetically related viruses have shown to be minimal. However, it has also been shown that the serum of subjects with a previous history of infection by other flaviviruses (especially dengue, yellow fever—including its

vaccine—and the West Nile virus) may present cross reactions⁽¹³⁾. Just as in the case of the virological diagnosis, the use of amniotic fluid or fetal tissue specimens might be useful, although to date these specimens are reserved for research settings.



For more detailed information: <http://bit.ly/1S96GsO>

V. CASE MANAGEMENT OF PREGNANT WOMEN WITH ZIKA

Since Zika virus infection is generally asymptomatic and is self-limited in the few cases that present with symptoms, patients often need no treatment and may not even see a physician. To date, no vaccine or specific therapy has been developed for Zika virus infection; consequently, treatment is aimed at relieving symptoms.

- i Rest and isolation:** To prevent any further transmission to other people, contact between Zika-infected patients and *Aedes* mosquitoes should be prevented, at least during the first week of the disease (viremic phase). The use of mosquito nets (insecticide-impregnated or not) is recommended; alternatively, people should stay in places protected with mosquito screens. Health care workers providing care to patients infected with Zika virus must protect themselves from mosquito bites by using repellents and wearing long sleeves and long trousers.
- ii Fever:** It is recommended to initially reduce the pregnant woman's fever with physical measures (damp cloths, light clothing, baths or showers with lukewarm water). When physical measures fail, pain relievers and antipyretics are suggested (acetaminophen or paracetamol is the first-line therapy).

Recommended dose: 500 mg orally every 6-8 hours; patients must be warned not to exceed 4,000 mg/day, since high doses may damage the pregnant woman's liver⁽¹⁷⁾

It is also advisable to warn pregnant women that many over-the-counter drugs contain acetaminophen, so the top-limit dose could inadvertently be surpassed.

- iii Headaches** should also be treated with acetaminophen at the dosages prescribed for fever management.



Do not use aspirin, as it increases the risk of bleeding; or NSAIDs, in case it is a dengue or chikungunya infection

- iv Itching:** Although there is no research either supporting or refuting the safety of topical products, clinical experience suggests that they are safe ⁽¹⁸⁾.

Topical application of calamine lotion or menthol-based aqueous creams

The safety profile of systemic treatment with H1 antihistamines is also high, so they may be used for intense itching ⁽¹⁹⁾.

- v Hydration:** Patients should be advised to drink plenty of fluids to replenish volume depletions through sweat, vomiting, and other insensible losses ⁽⁶⁾.

VI. REPERCUSSIONS OF ZIKA VIRUS INFECTION IN PREGNANCY

The association between Zika virus infection and the increased number of reports of congenital microcephaly and other congenital birth defects is a serious issue.

As of April 28, 2016, more than 1,000 cases of the congenital Zika syndrome have been reported in five countries across the region (1,198 in Brazil, 7 in Colombia, 3 in Martinique, 4 in Panama, and 2 in the United States)⁽²⁰⁾. Microcephaly is the sign that has attracted the greatest attention of the scientific community. There are also descriptions of cases of miscarriage and fetal death ^(6,21). In November 2015, the Brazilian Ministry of Health pointed to the link between the increased number of microcephaly in the northeastern regions of the country and the Zika virus infection, after detecting the viral genome in blood and tissue samples obtained from a newborn from the state of Pará that presented with microcephaly and other congenital malformations and died 5 minutes after birth. In April 2016, the CDC concluded that Zika virus is the cause of microcephaly and other defects in the fetal brain ^(6, 22, 23).

The term “congenital Zika syndrome” has been coined to include the following constellation of (clinical or ultrasonographic) signs and symptoms.

Congenital Zika syndrome	
Placental calcification	Cerebral anomalies with or without microcephaly
Oligo/anhydramnios	Reduced cerebral volume/cerebral atrophy
Abnormal cerebral arterial flow	Abnormal cortical development
Intrauterine growth restriction	Dysgenesis of the corpus callosum
Arthrogyposis	Cerebral and cerebellar calcifications
Cutis verticis gyrata	Cerebellar hypoplasia
Club foot	Subcortical calcifications
Cataracts and ocular calcifications	Fetal death



VII. MONITORING PREGNANT WOMEN IN SETTINGS WITH HIGH ZIKA VIRUS CIRCULATION

- i All pregnant women** should be advised to regularly attend their scheduled prenatal visits and take all tests recommended by the health team. There are many agents that can cause congenital defects, in particular microcephaly; pregnant women should be reminded to avoid alcoholic beverages, illicit drugs, and medications (unless prescribed by a health care professional). Likewise, they should be advised to avoid any contact with people with ongoing infectious conditions.

Since there is no specific treatment against this infection, prevention continues to be the key issue. Early capture of pregnant women continues to be important, so that all prenatal visits are in accordance with national standards and women are provided with information on the environmental measures (weekly destruction of mosquito breeding sites in and around dwellings) and personal measures recommended to reduce the risk of mosquito bites, as described in integrated vector management or in PAHO's epidemiological alert concerning Zika virus issued in May 2015 ⁽⁹⁾. Special attention should be paid to routine exams for syphilis, toxoplasmosis, cytomegalovirus, and rubella, which are relevant in case of congenital defects that require etiological confirmation.

As the infection may go unnoticed in a high percentage of people, at each visit pregnant women should be asked about the occurrence of any of the clinical signs and symptoms described in Table 1.

- ii Pregnant women with suspected Zika infection:** In addition to all the actions defined by the national guidelines for the monitoring of pregnancy, and depending on the risk level, the following are recommended:
 - ii a. Measure size of uterus and volume of amniotic fluid:** There is little evidence regarding the monitoring of pregnant women with Zika virus infection, but it is estimated that, as is the case with other congenital infections, there may be an association with a larger than normal uterus size (due to increased amniotic fluid) or a smaller than normal size (as a result of fetal growth defects or even fetal death) ⁽²⁴⁾.

ii b. **Evaluate fetal vitality**, including auscultation with a Pinard stethoscope (20 weeks) or Doptone at early gestational ages (14 weeks) to determine whether the fetus is still alive. At later gestational ages, perception of fetal movements may suffice ⁽²³⁾ (20 weeks). Obstetric ultrasound may serve the same purpose at early stages of pregnancy, as it can confirm embryonic vitality after the fifth week of gestation.

ii c. **Evaluation of fetal anatomy:** The ideal time for ultrasonography is at 18-22 weeks gestational age. However, if Zika infection is suspected, obstetric sonography is recommended in order to determine the situation immediately.

Obstetric sonography has shown that its capacity to diagnose secondary microcephaly (due to congenital infection) increases after 28 weeks gestational age (last trimester). Diagnostic accuracy is greater when other central nervous system defects are associated, such as encephalic microcalcification, ventricular expansion, hydrocephalus, and/or other defects including hepatomegaly, edema of the placenta, and fetal edema. All these are sonographic signs of congenital infection ^(25, 26). Microcephaly can only be confirmed after birth by measuring the newborn's head circumference ^(25, 26).¹

The two flow charts presented below should be used for the care of pregnant women. Figure 1 is for cases of women with current or recent clinical suspicion of Zika virus infection during pregnancy. Figure 2 is for monitoring women not suspected of Zika virus infection.

1. Refer to [link on microcephaly] for further details on the definition of microcephaly and the measurement technique to be used with newborns.

FIGURE 1: Flow chart for the care of women *with suspected* Zika virus infection.

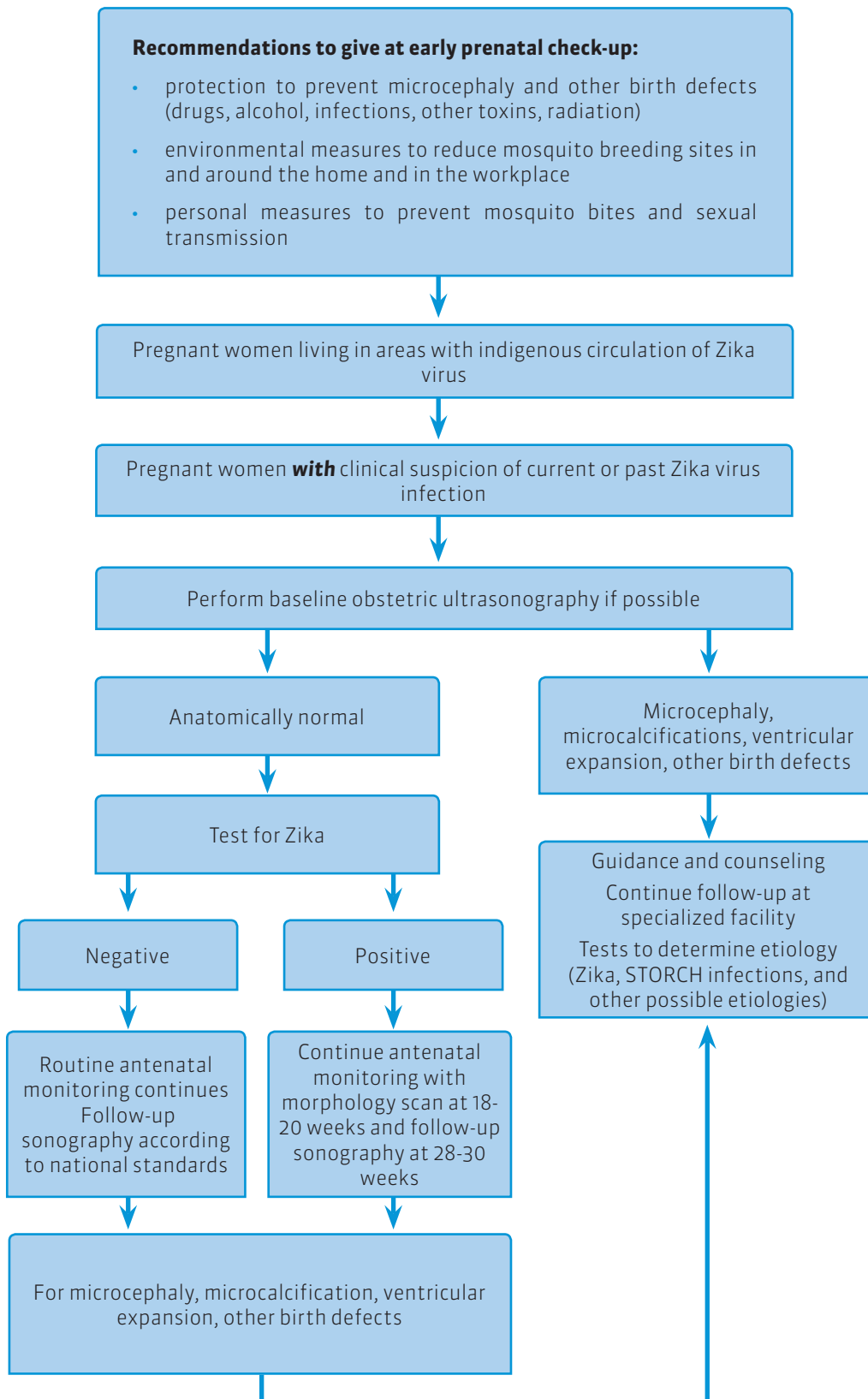
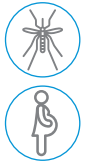
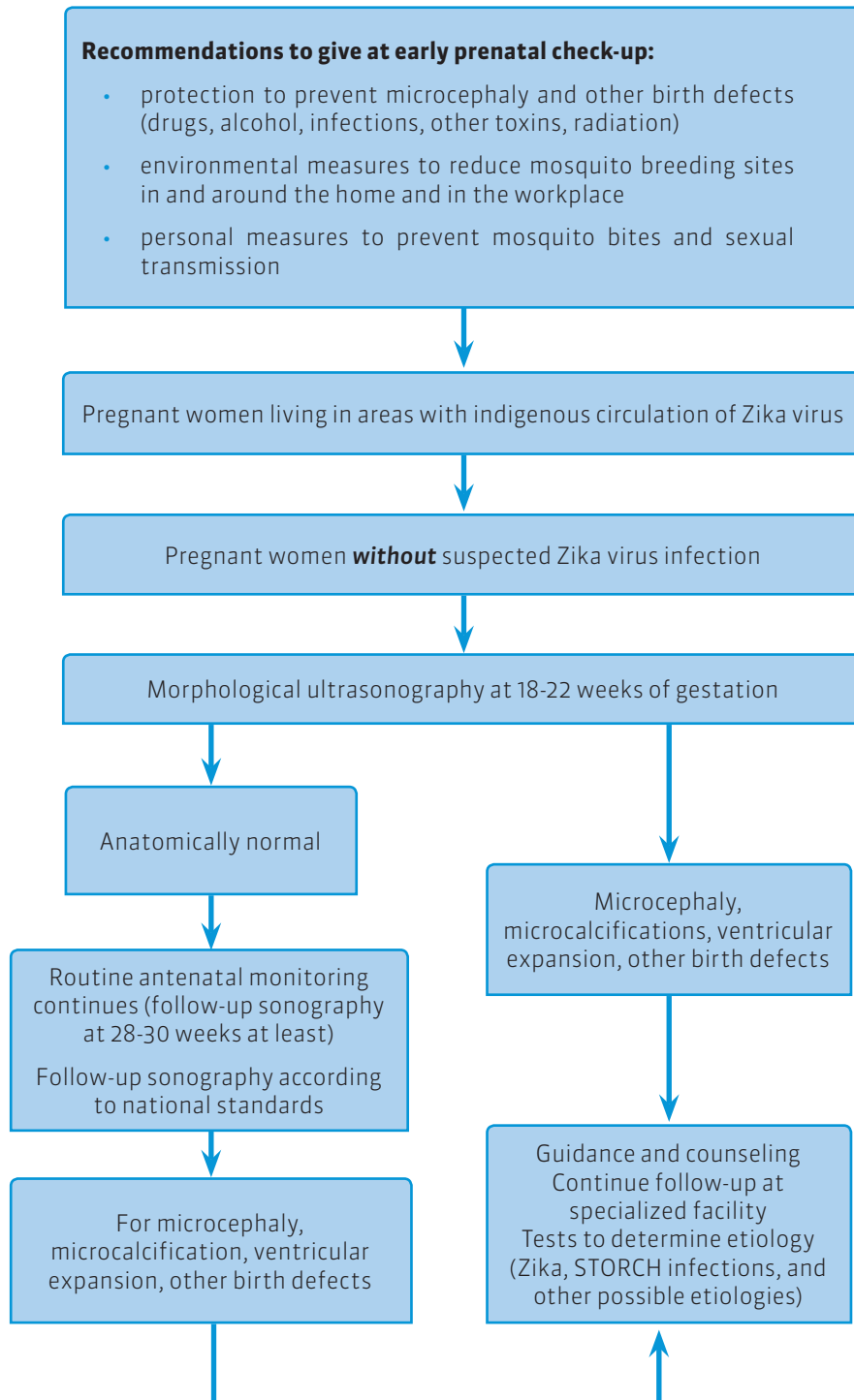


FIGURE 2: Flow chart for the care of women **without** suspected Zika virus infection



It should be kept in mind that use of these flow charts will depend on the availability of these services. Microcephaly can only be confirmed by measurement of the head circumference after birth.



VIII. WHEN TO SUSPECT MICROCEPHALY BASED ON ULTRASONOGRAPHY²

- i Head circumference:** Prenatal microcephaly may be suspected when the fetal head circumference is two standard deviations below the mean value for gestational age; however, most of these children have turned out to show normal intellectual function. Whenever possible, it is advisable to repeat the ultrasound after 15 days (preferably, one month). For individual clinical cases, health care professionals must be aware that when a measurement of the head circumference is three standard deviations below the mean value for gestational age, the correlation between microcephaly and impaired neurologic development is higher⁽²¹⁾. If a neonate whose mother had Zika virus infection during pregnancy is born normocephalic but with cerebral atrophy and ventricular enlargement, a thorough investigation of intracranial structures will be more relevant than merely obtaining a measurement of head circumference^(25, 27)

The correct determination of gestational age is relevant in all pregnancies, but it is even more important when investigating disorders that require anthropometric measurements based on gestational age. The ultrasound evaluation of the fetus's head circumference depends on the correct assessment of gestational age.

- ii Head circumference / femur length ratio or head circumference / abdominal girth ratio:** Tables are available with the values of these ratios based on gestational age. These ratios can be used to diagnose suspected microcephaly, but they have not proven to be any better than head circumference alone, when there is certainty about the gestational age. A recent study (using a 3-standard-deviations cut-off point) has established that this would lead to antenatal overdiagnosis of microcephaly; hence, it should be used with caution^(25, 27).

² Ultrasound devices have standardized tables for the various anthropometric measurements to be used, based on the characteristics of the local population.

IX. SPECIAL SITUATIONS

- i Death of the embryo or fetus:** The cause of the death of an embryo or fetus during pregnancy should always be investigated to prevent it happening in a future pregnancy. In areas where Zika virus circulates it is recommended to analyze tissue and/or placenta specimens in case of miscarriage or fetal death, in order to detect the virus.
- ii Tapping of amniotic fluid (amniocentesis) for testing:** This is an invasive technique that entails the risk of miscarriage and complications in the mother (infection); therefore, it should not be used routinely in all pregnant women. Confirmation of the virus in the amniotic fluid does not alter case management. At present, scientific research is underway in some settings including amniotic fluid testing, with informed consent and approval by local ethics committees.
- iii Other forms of mother-to-child transmission:** A woman infected close to term could potentially transmit the infection to her child during birth, but this has not been proven to date. Nor is there any proof of mother-to-child transmission during lactation, so there are no recommendations for suspending breast-feeding ⁽²⁸⁾.
- iv Traveling to areas with circulation of Zika virus:** To date, the Pan American Health Organization has not recommended that pregnant women or potentially pregnant women should limit travel to areas where an increase in the circulation of the virus has been detected. Women are recommended to discuss the issue with the providers in charge of their care, who, in turn, should provide the latest information available on the risks, particularly emphasizing personal protective measures to prevent mosquito bites and sexual transmission.



- v Postponing or interrupting pregnancy:** We do not know how long these Zika virus outbreaks may last. Any decision to postpone a pregnancy is a woman's human right.³ PAHO calls on public health authorities to guarantee that women have access to reproductive health services, including modern contraceptive methods; and that they are duly informed of personal protective measures to prevent mosquito bites, and of the risks that they may be exposed to. Women should also be informed about the support services that they can expect after giving birth. This information should be communicated to women in a culturally appropriate way and in language they can understand.

Detecting Zika virus during pregnancy is a challenge in most of the countries of the Region. At present, there is insufficient evidence to determine the possible risk of a pregnant woman contracting Zika or the risks that this infection could pose to her baby. Legislation in the Member States on the interruption of pregnancy must be taken into consideration when any decision is made.

- vi Pre-conception care:** The outbreak of Zika virus infection and the possibility of its vertical (mother-to-child) transmission increase the need to provide information about how to prevent this and other infections that can be vertically transmitted. This document discusses aspects related to the Zika virus; however, relevant information on other conditions is available in *Perinatal infections transmitted by the mother to her infant*: <http://bit.ly/1Upbxn7>.

3 Article 16 of the United Nations Convention to Eliminate All Forms of Discrimination against Women establishes that women have "the same rights to decide freely and responsibly on the number and spacing of their children and to have access to the information, education and means to enable them to exercise these rights." Regarding access to family planning methods, article 12 of the Convention establishes that "States Parties shall take all appropriate measures to eliminate discrimination against women in the field of health care in order to ensure, on a basis of equality of men and women, access to health care services, including those related to family planning." Article 14 refers to specific measures aimed at protecting women in rural areas and establishes that the States Parties will guarantee the right of these women to "have access to adequate health care facilities, including information, counselling and services in family planning." The Convention entered into force on September 3, 1981, and has been ratified by the following countries of the Region of the Americas: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, the Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Vincent and the Grenadines, Saint Lucia, Suriname, Trinidad and Tobago, Uruguay, and Venezuela

X. NOTIFICATION TO HEALTH AUTHORITIES

In ***countries with no autochthonous cases of Zika virus infection***, health care professionals are recommended to be alert to the occurrence of any cases of febrile rash illnesses of unknown origin (after having ruled out infections due to dengue, chikungunya, measles, rubella, parvovirus B19), and to perform laboratory testing for the detection of Zika virus.

In ***countries with autochthonous cases of Zika virus infection***, it is recommended to monitor the occurrence of fetal complications ranging from fetal death to the occurrence of defects, primarily those of the central nervous system, and to be vigilant about the detection of microcephaly. For further information on the surveillance of microcephaly in newborns in settings with risk of Zika virus circulation, please visit: <http://bit.ly/1S985Qh>.

If Zika virus infection is suspected, the professional must notify the center's health authorities, so the case can be reported to the national health authority, in compliance with the guidelines established in each country.

Considering the recent introduction of the Zika virus in the Americas, and for the sake of an integrated surveillance of the arbovirus, the national health authorities are requested to use the proper channels, as established in the International Health Regulations (IHR), to inform PAHO/WHO on the laboratory-confirmed cases of Zika virus infection recorded in the countries and territories of the Region of the Americas.

In addition, and seeking to contribute to an understanding of the potential sequelae of this virus, PAHO/WHO requests that the Member States report any increases in congenital abnormalities observed in newborns, and which cannot be explained by a known cause.

To that end, cases must be reported after the first contact between a woman and her local health care professionals, as established in the guidelines defined by the national health authority.



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