Pregnancy management in the context of Zika virus

Interim guidance

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1. Introduction

1.1 Background

Zika virus is a flavivirus that is primarily transmitted by infected *Aedes* mosquitoes. This vector also transmits dengue and chikungunya viruses and is commonly found in tropical and sub-tropical environments in Africa, the Americas, Asia and the Pacific. Although Zika virus was first identified in humans in 1952, very few outbreaks were documented prior to 2015. Human infection is often asymptomatic, and symptoms are usually mild and self-limiting. While the usual characteristics of human infection have not changed, the recent association between Zika virus infection and potential congenital microcephaly and Guillain-Barré Syndrome in some affected areas[1] has escalated this issue to a Public Health Emergency of International Concern.[1-3]

1.2 Rationale and objectives

The mosquito vector that carries the Zika virus thrives in warm climates and particularly in areas of poor living conditions. Pregnant women living in or travelling to such areas are at equal risk as the rest of the population of being infected by viruses borne by this vector. Maternal infection with Zika virus may go unnoticed as some people will not develop symptoms. Although Zika virus infection in pregnancy is typically a mild disease, an unusual increase in cases of congenital microcephaly, Guillain-Barré syndrome and other neurological complications in areas where outbreaks have occurred,[1,2] has significantly raised concern for pregnant women and their families, as well as health providers and policy-makers.[4]

While the association between Zika virus infection and fetal microcephaly is still being investigated,[5] maternal-fetal transmission throughout pregnancy has been documented.[6-8] Laboratory isolation of the virus in the neurologic tissues of infants with microcephaly has further added to the suspicion of causality.[8] It is also unclear whether Zika virus infection contributes to spontaneous pregnancy losses and stillbirths, although Zika virus RNA has been detected in products of conception following miscarriage by infected women.

The aim of this document is to provide interim guidance for interventions to reduce the risk of maternal Zika virus infection and to manage potential complications during pregnancy. This guidance is based on the best available research evidence and covers areas prioritized by an international, multidisciplinary group of health care professionals and other stakeholders. Specifically, it presents guidance for preventing Zika virus infection; antenatal care and management of women with infection; and care during pregnancy for all pregnant women living in affected areas, with the aim of optimizing health outcomes for mothers and newborns. The guidance is intended to inform the development of national and local clinical protocols and health policies that relate to pregnancy care in the context of Zika virus transmission. It is not intended to provide a comprehensive practical guide for the prevention and management of Zika virus infections.

1.3 Scope of the guidance

This guidance is relevant to all pregnant women residing in areas of Zika virus transmission, and particularly for pregnant women suspected of being at risk of, or diagnosed with Zika virus infection. It does not cover non-pregnant women, or the management and follow-up of newborns.

1.4 Target audience

The primary audience for this guidance includes health professionals who are directly providing care to pregnant women including obstetricians, general practitioners, midwives and nurses. The guidance may also be used by those responsible for developing national and local health protocols and policies, as well as managers of maternal and child health programmes, especially in regions with unusual increases in adverse fetal and newborn outcomes suspected to be associated to Zika virus infection.

2. Recommended practices

2.1 Preventive measures

Infection prevention measures for pregnant women are the same as those recommended for the general population. However, the importance of preventive measures should be emphasized at every contact with a pregnant woman. Health care professionals should promote the following measures with pregnant women and their families, and in the community.

Vector control: Environmental measures should be undertaken to reduce vector density. As mosquito control is the only measure that can successfully interrupt

transmission of viruses such as Zika, dengue, and chikungunya, every effort should be made to identify and destroy potential mosquito breeding sites from homes and workplaces.[a]

Personal protection measures: The following interventions are recommended for the general population and for pregnant women in particular:

- Protection of the skin from exposure to mosquitoes by wearing clothes that cover as much of the body as possible (e.g. long sleeves, long trousers or skirts)
- Use of mosquito bed nets, including when sleeping during the daytime
- Use of mosquito mesh/nets/screens on windows and doors
- Use of insect repellents approved by local health authorities (e.g. DEET or Icaridin-based insect repellents; to date, these are the repellents that have been found to be safe during pregnancy). Repellent should be applied on exposed body areas, and even over clothes, whenever indicated, and re-applied as indicated by the manufacturer on the product label.
- Use of the above personal protection measures by individuals infected with Zika, dengue, and or chikungunya virus should be encouraged to avoid spread of infection to uninfected individuals. These measures should be implemented at least during the first week of onset of symptoms (viraemic phase).
- To prevent potential sexual transmission of Zika virus, sexual partners of pregnant women, living in or returning from areas of ongoing Zika virus transmission, should use safer sexual practices (including correct and consistent condom use) or abstain from sexual activity for the duration of the pregnancy.[b]

2.2 Diagnosis

Clinical presentation: There is no known difference in the clinical presentation of Zika virus-infected pregnant and non-pregnant women. Zika virus infection is asymptomatic in the majority of cases. In symptomatic cases, symptoms typically appear a few days after the bite of an infected mosquito. Most people with Zika virus disease will get a slight fever and rash. Others may also get conjunctivitis, joint pain, headache, muscle pain, and feel tired. These symptoms last between 2–7 days and are generally mild and self-limiting.

Some countries with active Zika virus transmission have reported increased occurrence of neurological syndromes, including, but not limited to Guillain-Barré syndrome. Therefore, it is reasonable to investigate for Zika virus infection in any pregnant woman presenting with neurological complications.

Case definition of Zika virus disease: Interim case definitions for Zika virus disease have been developed by WHO and can be accessed at http://www.who.int/csr/disease/zika/case-definition/en.

Diagnosis: The diagnostic steps recommended for pregnant women are the same as those recommended for the general population. Diagnosis requires detection of the virus using reverse transcription polymerase chain reaction (RT-PCR) in maternal serum within five days of onset of symptoms. Zika virus may also be detected in urine with the period of shedding lasting up to three weeks after the onset of symptoms. Zika virus has also been detected in saliva but the period of virus shedding appears to be the same as in serum. RT-PCR can also identify viral RNA in amniotic fluid, although the sensitivity and specificity of this test for detecting congenital infection is currently uncertain.

Serological tests can also be performed to diagnose Zika virus infection with IgM antibodies detected through enzyme linked immunosorbent assays (ELISA) or immunofluorescence from the fifth day following onset of symptoms. Following an individual's first infection with a flavivirus, cross reactions with other genetically related viruses in serological tests are minimal. However, the serum of individuals with a previous history of infection by other flaviviruses has an increased likelihood of cross reactions. Considering that a substantial proportion of the population living in areas with ongoing Zika virus transmission can be assumed to have had previous contact with other flaviviruses (especially dengue, and yellow fever, including its vaccine), cross-reactions and false positive results are possible. Careful attention should be given to ensuring that any serological test that is used to guide the management of pregnancy has been validated by a competent national or international authority.

2.3 General care and symptomatic treatment

To date, no vaccine or specific therapy has been developed for Zika virus infection. Consequently, treatment is aimed at relieving symptoms if they occur.

Rest and use of personal protection measures: Symptomatic pregnant women with Zika virus infection should be advised to rest and use the personal protection measures described above to reduce the likelihood of viral transmission to other people, particularly during the first week of the disease (viraemic phase).

[a] Additional information on vector control can be found at http://www.who.int/mediacentre/factsheets/zika/en/

[b] Additional information on prevention of potential sexual transmission can be found at http://www.who.int/csr/resources/publications/zika/sexual-transmission-prevention/en/

Fever: Fever should be managed with physical cooling measures (e.g. damp cloths, light clothing, baths or showers) and acetaminophen (paracetamol). The use of aspirin or other NSAID agents should be avoided until dengue viral infection has been excluded.

Headache: Headache should also be treated with acetaminophen at the dosages prescribed for fever management.

Itching: Although there is no research either supporting or refuting the safety of topical products for itchy rash during pregnancy, there is clinical experience suggesting their safety. The safety profile of systemic treatment with antihistaminic agents is also high. Topical applications of calamine lotion or menthol-based aqueous agents or oral loratadin may be used.

Hydration: Affected pregnant women should drink plenty of fluid to avoid volume depletions through sweat, vomiting, and other insensible losses that can accompany the viraemic phase.

2.4 Care for pregnant women living in areas with ongoing Zika virus transmission

Testing for Zika virus infection is currently recommended for pregnant women presenting with a history of Zika virus disease symptoms or signs. In view of the potential burden on currently available local health resources, WHO does not at this time recommend testing all pregnant women in areas of Zika virus transmission. However, health professionals should consider offering a first trimester ultrasound scan, where possible, to all women presenting for antenatal care to accurately date the pregnancy and perform a basic fetal morphology assessment.

All pregnant women should be advised to present for their scheduled antenatal visits in accordance with national standards and to comply with the recommendations of their health care providers. Women should be counselled to present early for treatment and diagnostic work up if they develop any of the symptoms of Zika virus infection described above. During all antenatal visits, all women should be provided with information on standard environmental and individual protection measures as described above. Routine investigations should be carried out to exclude syphilis, toxoplasmosis, cytomegalovirus, rubella, and herpes which are also known causes of intrauterine infection and congenital birth defects.

Annex 1 provides a decision-chart for the care of pregnant women living in areas with ongoing Zika virus transmission. At each visit, all pregnant women should be asked about any of the symptoms or signs of Zika virus infection referenced above, since their last antenatal visit. If this is their first antenatal contact, they should be questioned about the occurrence of these symptoms during the current pregnancy.

Regardless of a history of illness consistent with Zika virus infection, all women in areas of ongoing Zika virus transmission should receive routine antenatal care and be requested to have a fetal anomaly scan between 18 and 20 weeks or at the earliest possible time if the first visit occurs after 20 weeks. Careful attention should be paid to the fetal central nervous system to identify any abnormalities, including microcephaly and other intracranial structural deformities.

Women with a history of clinical illness who test negative for Zika virus infection but who have no evidence of fetal microcephaly or other brain abnormalities on ultrasound, should continue to receive routine antenatal care. A repeat fetal ultrasound in late second or early third trimester, preferably between 28 and 30 weeks of gestation, is recommended to identify fetal microcephaly and/or other brain abnormalities when they are much easier to detect. This is because it is possible for the mother to be infected and for the fetus to be affected after an initial negative Zika virus test and normal ultrasound examination.

Where feasible, amniocentesis should be considered for women with negative Zika virus test results but abnormal fetal brain ultrasound findings, either at the 18–20 week anomaly scan or 28–30 week repeat scan, to screen for genetic abnormalities and congenital infections including Zika virus. It should be noted that the sensitivity and specificity of amniocentesis for detecting congenital Zika virus infection is currently uncertain.

The occurrence of a positive Zika virus test in maternal serum (or amniocentesis specimen) and ultrasound findings of fetal microcephaly and/or other brain abnormalities should raise a suspicion of Zika virus related fetal abnormalities. For women in this category, history and further investigations can be used to determine whether the abnormalities are related to Zika virus or other possible causes such as congenital infections or genetic syndromes.

2.5 Antenatal evaluation of Zika virus related fetal microcephaly and/or other brain abnormalities

Ultrasound investigations to identify, monitor, or exclude fetal brain abnormalities, particularly microcephaly, are recommended for all pregnant women living in areas with ongoing Zika virus transmission. All women should be offered an 18–20 week anomaly scan by a health care provider with experience in prenatal ultrasound diagnosis. Women should be offered a first trimester ultrasound, where feasible, to accurately determine gestational age, as ultrasound investigation of fetal abnormalities often

requires anthropometric measurements based on gestational age.

In the context of Zika virus transmission, ultrasound examination should be directed at identifying fetal microcephaly, and/or other brain abnormalities such as ventriculomegaly, calcifications, abnormal sulcation and gyration, brain atrophy, callosal dysgenesis, failure to visualize different portions of the brain, microophthalmia, and eye calcifications which have been reported in affected pregnancies.[7] While the complete picture of congenital abnormalities that may result from Zika virus fetal infection is still unclear, existing knowledge of other congenital infections (e.g. CMV, toxoplasmosis, herpes) suggests that infected fetuses can present a much wider spectrum of the disease, ranging from being completely asymptomatic to severe involvement of the brain and other organs and even intrauterine fetal death. Therefore, searching for early appearance of subtle signs of fetal brain abnormalities in association with a positive or inconclusive test for Zika virus is likely to facilitate early diagnosis and appropriate care.

Fetal microcephaly is a condition in which the fetal head is significantly smaller than expected for gestational age and sex and may be associated with abnormal brain development. Health professionals and pregnant women should be aware that prenatal ultrasound diagnosis of this condition is not straightforward and most cases of microcephaly diagnosed at birth or later in life may not be identified during pregnancy.[9] While there is no absolute quantitative cut-off, fetal head circumference at various levels below the average for the reference population is commonly applied to diagnose fetal microcephaly, with smaller head circumference increasing the probability of the diagnosis.[10,11]

In fetuses with head circumference two standard deviations below the mean for gestational age, microcephaly should be suspected, although in the absence of serious brain abnormalities, normal neuropsychological development is common in most affected fetuses after birth. For fetuses with head circumference three standard deviations below the mean for gestational age, the correlation between microcephaly and impaired neurologic development is higher. Fetal head circumference five standard deviations below the mean for gestational age is an indication of severe reduction in intracranial size, and an ultrasound diagnosis can be made with a reasonable level of confidence.[12] These quantitative ultrasound examinations can be made by a sonologist with basic experience in fetal biometric examinations, although identification of associated brain abnormalities may require additional training. As these measurements are related to the average fetal dimensions for gestational age, it is critical to ensure that pregnancies are accurately dated and that the appropriate reference fetal growth curve for the population is used to avoid misdiagnosis.

Case definition of Zika virus-related fetal microcephaly: To facilitate classification of fetal microcephaly in the context of ongoing Zika virus transmission, the WHO interim guidance panel adopted the following case definition for Zika virus-related fetal microcephaly:

- Fetal microcephaly with a molecular or epidemiological link to Zika virus in the absence of other conditions that are known to cause microcephaly.

A molecular or epidemiological link with Zika virus is defined as:

- The pregnant woman is a confirmed case of Zika virus disease; **or**
- The pregnant woman had sexual contact with a confirmed case, or a history of symptoms or signs consistent with Zika virus infection and residing/travelling in an area with ongoing Zika virus transmission during her pregnancy; **or**
- Presence of Zika virus in amniotic fluid (identified through amniocentesis and RT-PCR assay); **or**
- Presence of Zika virus in fetal brain tissue (identified postmortem through RT-PCR assay).

Other known causes of microcephaly that should be ruled out include other congenital infections, toxoplasmosis, rubella, herpes, syphilis, cytomegalovirus and HIV; exposure to toxic drugs, chemicals and radiation; genetic abnormalities e.g. Down syndrome; fetal malnutrition and placental insufficiency.

2.6 Care for pregnant women with possible Zika virus related fetal microcephaly and/or other brain abnormalities

Where resources exist, pregnant women with ultrasound evidence of suspected or confirmed fetal microcephaly and/or other brain abnormalities should be referred for specialized care, regardless of the underlying cause. If brain abnormalities are confirmed on ultrasound and a Zika virus test is positive in maternal serum or amniocentesis, then it is possible that the abnormalities are related to Zika virus.

Head circumferences more than two, three and five standard deviations below the mean for gestational age have been used as diagnostic criteria for fetal microcephaly. As the head circumference gets smaller, the likelihood of other brain abnormalities and consequently a poorer prognosis is more likely. In such situations, the woman – and her partner if she wishes – should receive individualized care and counselling. Depending on the severity and certainty of the fetal brain abnormalities and associated prognosis, this could range from specialized

antenatal care and serial ultrasound follow-up to monitor any progression of the abnormalities, to a discussion of the potential next steps in managing the pregnancy. It is important to ensure that an affected pregnant woman receives accurate and evidence-based information on the prognosis of the identified abnormalities. The woman – and her partner if she so wishes – should be offered non-directive counselling so that she, in consultation with her health care provider, can make a fully informed choice about the next steps in the management of her pregnancy.

Women who carry their pregnancy to term must receive appropriate care and support to manage anxiety, stress and the birth environment. Plans for care and management of the baby soon after birth should be discussed with the parents in consultation with a paediatrician or paediatric neurologist where available.

Women who wish to discontinue their pregnancy should receive accurate information about their options to the full extent of the law,[13] including harm reduction where the care desired is not readily available.

All women, whatever their individual choices with respect to their pregnancies, must be treated with respect and dignity.

3. Guidance development

3.1 Acknowledgements

This interim guidance was developed by the WHO Department of Reproductive Health and Research (RHR), and Department of Maternal, Newborn, Child and Adolescent Health in collaboration with the WHO Regional Office for the Americas. A steering group consisting of A. Metin Gülmezoglu, Olufemi Oladapo, Clara Menendez (WHO/RHR), Bremen De Mucio, Rodolfo Gomez (AMRO), and João Paulo Souza (University of Sao Paulo, Ribeirão Preto, Brazil) managed the guidance development process.

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3.2 Guidance development methods

This guidance builds on existing recommendations from WHO and other international agencies. The guideline development process consisted of: identification of priority questions; rapid literature search and retrieval of evidence; assessment and synthesis of available evidence; and agreement on recommendations. The steering group used the available evidence and expert consultations to draft recommendations of clinical practices and a decision-chart for testing and care in the context of Zika virus transmission. WHO convened a virtual technical consultation on 16 February 2016 where the GDG reviewed and approved the recommendations based on available evidence and expert opinion.

3.3 Declaration of interests

All GDG members completed a standard WHO Declaration of Interests (DOI) form before participating in the technical consultation or any activities related to development of the guidance. All findings from the received DOI statements were managed in accordance with the WHO guidelines on a case-by-case basis. Participants at the technical consultation also made DOI statements prior to the consultation and no conflicts were identified.

3.4 Review date

These recommendations have been produced under WHO emergency procedures and will remain valid until August 2016. The Department of Reproductive Health and Research at WHO Geneva will be responsible for reviewing this guidance at that time, and updating it as appropriate. WHO welcomes queries and suggestions regarding the content of this guidance. Please email suggestions to mpa-info@who.int.

4. References

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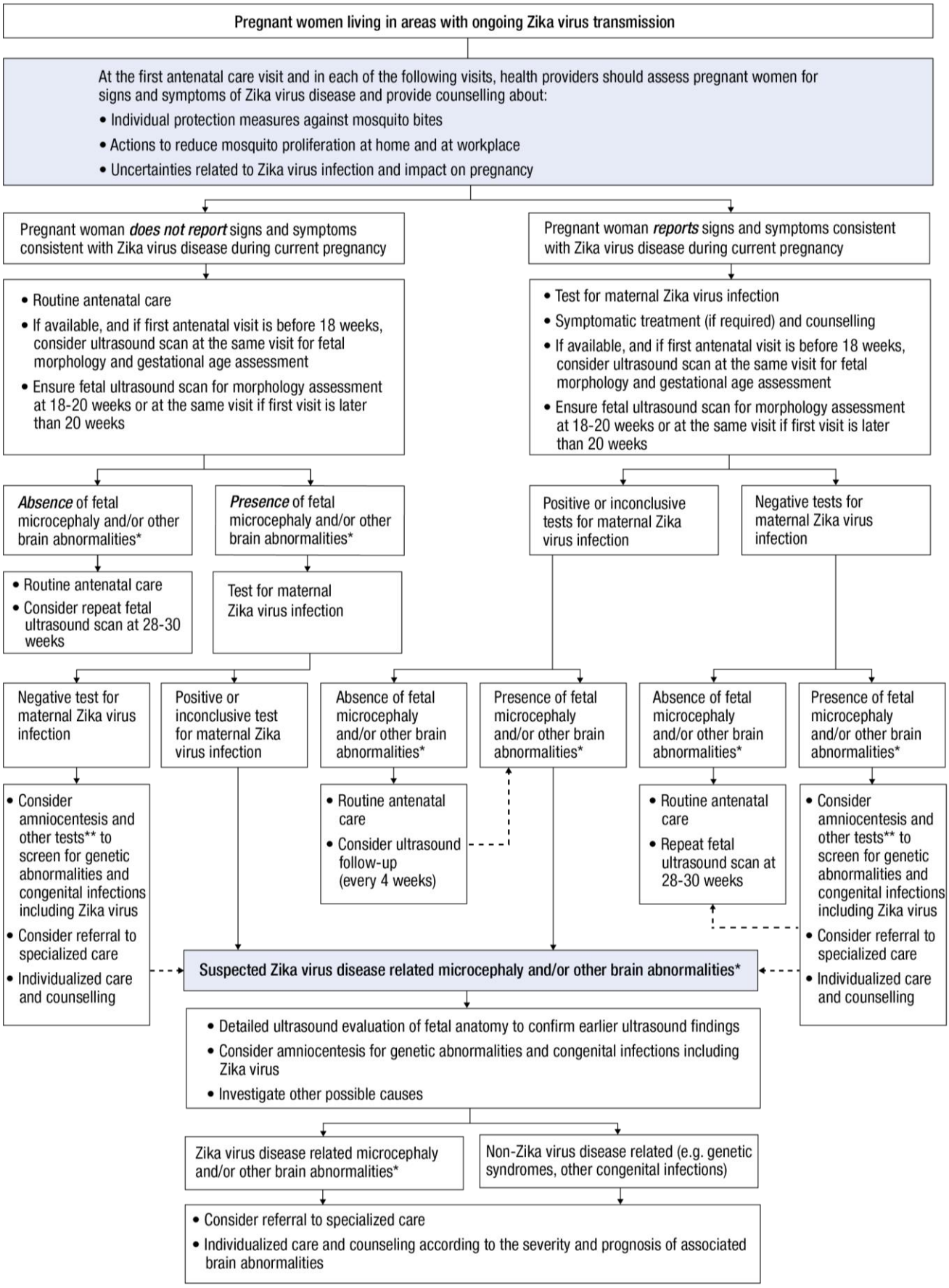
Annex 1: Decision-chart for the care of pregnant women living in areas with ongoing Zika virus transmission.



* Includes ventriculomegaly, calcifications, abnormal sulcation and gyration, brain atrophy, callosal dysgenesis, failure to visualize different portions of the brain, cerebellar abnormalities, microophthalmia, eye calcifications, or arthrogryposis.

** Syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex infections.