



**Pan American
Health
Organization**



**World Health
Organization**

REGIONAL OFFICE FOR THE **Americas**

**Provisional remarks on Zika virus infection in pregnant
women:**

Document for health care professionals

January 25, 2016

Pan American Health Organization / World Health Organization

Montevideo, 2016

CONTENTS

I.	INTRODUCTION.....	4
II	AIM / OBJECTIVES OF THE DOCUMENT	5
III	PREVENTION OF ZIKA VIRUS INFECTION.....	6
	i. Environmental measures	6
	ii. Personal protection measures	6
	iii. Patient isolation	7
IV.	ZIKA VIRUS INFECTION DURING PREGNANCY	7
	i. Clinical issues:.....	7
	ii. Diagnosis.....	8
	ii a. Diagnosis.....	8
	ii b. Differential clinical diagnosis.....	8
	ii c. Confirmed diagnosis.....	8
	ii c1. Virological diagnosis.....	9
	ii c2. Serological diagnosis	9
V.	CASE MANAGEMENT OF PREGNANT WOMEN WITH ZIKA.....	10
	i Rest and isolation.....	10
	ii Fever	10
	iii Headaches.....	11
	iv Itching.....	11
	v Hydration	11
VI	REPERCUSSIONS OF ZIKA VIRUS INFECTION IN PREGNANCY	12
VII	MONITORING OF PREGNANT WOMEN	13
	i All pregnant women	13
	ii Pregnant women with suspected Zika infection	14
	ii a. Measure size of uterus and volume of amniotic fluid:.....	14
	ii b. Evaluate fetal vitality.....	14
	ii c. Evaluation of fetal anatomy	14
VIII	WHEN TO SUSPECT MICROCEPHALY WITH ULTRASONOGRAPHY	15
	i Head circumference.....	15
	ii Head circumference / femur length ratio or Head circumference / abdominal girth ratio:.....	16
IX	SPECIAL SITUATIONS	16
	i Death of the embryo or fetus.....	16
	ii Tapping of amniotic fluid (amniocentesis) for testing:	16
	iii Other forms of mother-to-child transmission:.....	17
	iv Traveling to areas with circulation of Zika virus:	17
	v Postponing pregnancy:.....	17
	vi Interruption of pregnancy:.....	17
	vii Pre-conception care.....	18
X	NOTIFICATION TO HEALTH AUTHORITIES.....	18
XI	REFERENCES	20

This document was developed by PAHO/WHO based on the 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.

For any queries or comments, please contact the Pan American Health Organization: Dr. Bremen De Mucio demuciob@paho.org (cc) Mrs. Magdalena Bonasso bonassom@paho.org

I. INTRODUCTION

The Zika virus is a flavivirus transmitted by a mosquito that belongs 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 technique of the Real Time Polymerase Chain Reaction (RT-PCR) applied to the amniotic fluid of two pregnant women in Paraiba, 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 recent study by Fiocruz-Paraná using histochemistry confirmed the presence of the virus in the placenta ⁽⁸⁾. Having a similar situation been 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 centralized at a Web site specifically dedicated to the issue, www.paho.org/viruszika.

Twenty countries and territories have confirmed autochthonous circulation of Zika Virus in the Americas from January 22 to January 2016: Brazil, Barbados, Bolivia, Chile (Easter Island), Colombia, Ecuador, El Salvador, Guatemala, Guiana, French Guiana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, and Venezuela (www.paho.org/viruszika).

Given the introduction of this new virus in the Americas and its potential association with microcephaly and other abnormalities, this document presents provisional considerations on Zika virus infection in pregnant women.

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 therapy and monitoring of pregnant women, and notification of cases to the competent health authorities.

The information presented in this document was updated on January 22, 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; however, the importance of prevention measures should be emphasized because of the impact of such an infection in pregnant women. Health care professionals should promote the measures below, 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 only 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⁾.

ii. **Personal protection measures:** Health care professionals should insist on measures to reduce to a minimum the vector's contact with patients infected with dengue, chikungunya or Zika virus, in an attempt to put an end to the spread of infection. Below is a list of recommendations for the entire population, but particularly for pregnant women ⁽⁶⁾:

- Cover your skin with long sleeves, trousers, and stockings.
- Use bed mosquito nets, impregnated with insecticide or insecticide-free.
- Use mosquito mesh/nets/screens on windows and doors.
- Use any of the repellents recommended by the health authorities (DEET, Picaridin, Icaridin). To date, these are the repellents that offer the highest safety levels during pregnancy and breastfeeding. They should be applied on exposed body areas, and even over clothes, whenever

indicated, and re-applied as suggested by the manufacturer on the product label. The repellent will have no protective effect unless it is used following the manufacturer's recommendations.

- Look for and destroy any potential foci favoring the proliferation of mosquitoes, and eliminate them from homes.

iii. Patient isolation. Infected people should be isolated to prevent the transmission of the virus to other people (including pregnant women) by preventing contact between the patient infected with Zika virus and mosquitoes, at least during the first week of the disease (viremic phase), applying the above-described personal protection measures ⁽⁶⁾.

IV. ZIKA VIRUS INFECTION DURING PREGNANCY

i. Clinical issues: no clinical differences have been described between pregnant and non-pregnant women. After the infected mosquito bites the patient, the symptoms of the disease typically appear after a three- to twelve-day incubation period. Overall, the cases are usually not fatal. Infection may progress asymptotically (70-80% of cases), or present with the clinical features below ⁽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

* This is one of the most distinctive symptoms of Zika virus infection that should be considered for diagnosis and entered in the pregnant woman's medical record. Symptoms last 4-7 days, and are usually

self-limited ⁽¹⁾.

In the context of Zika virus circulation, some 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 there is no proven evidence of the causal relation of such cases with Zika virus, that hypothesis cannot be dismissed ⁽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 ⁽¹³⁾.

ii a. Diagnosis is based on clinical suspicion, usually related to one or several of the above-described symptoms. There will be stronger grounds for suspicion if the subject had been in an area or territory where the vector was present in the days before presenting with symptoms; suspicion will be further strengthened if any cases of viral infection have been verified in the area; this will be a stronger element leading to a presumptive diagnosis of Zika virus infection.

ii b. Differential clinical diagnosis will be established with other infections causing rash and fever, particularly those caused by flaviviruses such as dengue, chikungunya or West Nile, among others.

ii c. Confirmed diagnosis: 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 drawn.

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 ⁽¹³⁾. Furthermore, viral RNA may be found in saliva or urine specimens collected during the first 3 to 5 days following the onset of symptoms ⁽¹⁴⁾. 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 ⁽¹³⁾.

ii c2. Serological diagnosis detects Zika virus anti-IgM antibodies through ELISA or immunofluorescence. This cannot be achieved until 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, there is almost no need for therapy. 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 using repellents and wearing long sleeves and long trousers.

ii Fever: There is evidence that during pregnancy, fever is associated with birth defects ⁽¹⁵⁾; as there are no drugs considered to be 100% safe, the recommendation is 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 anti-pyretics must be added, acetaminophen or paracetamol being the first-line therapy.

Recommended dose: 500 mg orally every 6 or 8 hours; patients must be warned not to exceed 4,000 mg/day, since high doses may damage the pregnant woman's liver ⁽¹⁶⁾

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 will also be treated with acetaminophen at the dosages prescribed for fever management.

Do not use aspirin, as it increases the risk of bleeding, nor NSAIDs, because of their effects in infections caused by dengue or chikungunya

iv Itching, although there is no research either supporting or refuting the safety of topical products, there is clinical experience suggesting their safety (17).

Topical application of calamine lotion or menthol-based aqueous creams

The safety profile of systemic treatment with antihistaminic agents is also high, so the different forms of Loratadin may be recommended (18).

Loratadin (orally): 5 to 10 mg every 12 hours

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 birth defects is a serious issue.

Multiple cases of central nervous system abnormalities related to Zika outbreaks have been reported both in Brazil and French Polynesia. 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, 19). 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 the blood and tissue samples obtained from a newborn of the state of Para that presented with microcephaly and other congenital malformations, and died 5 minutes after birth. However, this association has not been confirmed by other researchers ⁽⁶⁾.

VII MONITORING OF PREGNANT WOMEN

i All pregnant women should be advised to regularly attend their scheduled prenatal visits and to take all the tests indicated by the health team. There are many agents that can cause congenital defects, in particular microcephaly; consequently 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; at those visits, women should be provided with information on the environmental and individual measures recommended to reduce the risk of bites by the mosquito that transmits the Zika virus, as described in integrated vector management or in PAHO's epidemiological alert concerning Zika virus issued in May 2015 ⁽¹⁾. Special attention must be paid to routine exams for syphilis, toxoplasmosis, cytomegalovirus, and rubella, which will be 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 on the monitoring of pregnant women with Zika virus infection, but it is estimated that, as is the case with other congenital infections, it might be associated 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) ⁽²⁰⁾.

ii b. Evaluate fetal vitality, including auscultation with a Pinard stethoscope (20 weeks) or Doppler at early gestational ages (14 weeks) to determine whether the fetus is still alive. At later gestational ages, perception of fetal movements may suffice ⁽²⁰⁾ (20 weeks). Obstetric ultrasound may serve that purpose at early stages of pregnancy (5 weeks).

ii c. Evaluation of fetal anatomy: Ultrasonography in the final trimester might rule out microcephaly and other abnormalities in the fetuses of women that were exposed to the Zika virus. Microcephaly can only be confirmed after birth by measuring the neonate's head circumference ^(21 – 22).¹

Obstetric ultrasound is unable to confirm the existence of microcephaly, but it may suggest it.

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

Obstetric ultrasonography has shown that its capacity to diagnose secondary microcephaly (in this case due to a connatal infection), increases after the 28th week of gestation (last trimester). The diagnostic approximation will be stronger when associated with other defects of the central nervous system, including brain microcalcifications, enlarged ventricles, hydrocephaly and/or other defects, including, but not limited to an enlarged liver, edema of the placenta and fetal edema. All these are sonographic signs of connatal infection ^(21 - 22).

VIII WHEN TO SUSPECT MICROCEPHALY WITH 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 a normal intellectual function. Whenever possible, it is advisable to repeat the ultrasound after 15 days, to perform anthropometric measurements. 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⁾.

The correct determination of gestational age is relevant in all pregnancies, but 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.

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

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 measurements 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 ⁽²¹⁾.

Most countries have national guidelines establishing that ultrasonography should be conducted in the final trimester in low-risk pregnancies. When microcephaly is suspected, based on an isolated scan, ultrasound monitoring may be warranted to measure the development of the head circumference and other fetal anthropometric data, as well as to detect the occurrence of other congenital defects, when the needed resources are available.

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 recommendable 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 ⁽²³⁾.

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 their doctors, and health care professionals are recommended to provide the latest information available on the risks, particularly emphasizing personal protective measures to prevent mosquito bites.

v Postponing pregnancy: Aware that the decision on the right time to become pregnant is an individual right, and since we do not know how long Zika virus outbreaks may last, the Pan American Health Organization insists that women should be informed about personal protection measures and the potential risks involved.

vi Interruption of pregnancy: On the basis of the cases reported in Brazil, research studies have been launched to characterize the cases and potential consequences.

In the framework of reproductive rights, the DECISION ON WHETHER OR NOT TO INTERRUPT PREGNANCY CORRESPONDS SOLELY TO THE WOMAN AND HER FAMILY.

Each country has its own specific set of norms and legislation

governing the interruption of pregnancy, and health care systems will provide proper care to women and their newborns.

vii Pre-conception care: The occurrence of Zika virus infection and its vertical (mother-to-child) transmission reaffirms the need to provide information about how to prevent this and other infections that have vertical transmission potential. This document discusses the aspects related to the Zika virus; however, information on other conditions is available in the document on perinatal infections transmitted from mother to child: <http://bit.ly/1Upbxn7>

X NOTIFICATION TO HEALTH AUTHORITIES

In those *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 the Web site: <http://bit.ly/1S985Qh>

If a 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 the knowledge of the potential sequelae of this virus, PAHO/WHO requests the Member States to report any increases in congenital abnormalities observed in newborns, and which cannot be explained by a known cause.

To that end, the case needs to be reported, as established in the guidelines defined by the national health authority, as soon as the user contacts the local health care professionals for the first time.

XI REFERENCES

- 1.- Pan American Health Organization. Zika virus infection. Epidemiological alert. May 7, 2015. Available at: <http://bit.ly/1PD5YNI>
- 2.- Chile. Ministerio de Salud. Instituto de Salud Pública confirma el primer caso en el país de infección por virus Zika (ZIKAV) (07/03/2014). Available at: <http://www.ispch.cl/noticia/20750>
- 3.- Brasil. Ministério da Saúde. Confirmação do Zika Vírus no Brasil, [Internet]. Brasília: Ministério da Saúde, 2015. Available at: <http://bit.ly/1E9j3Z2>
- 4.- Secretaría de Salud del estado de Pernambuco. Ministério da Saúde investiga aumento de casos de microcefalia em Pernambuco. Available at: <http://bit.ly/1nLU11W>
- 5.- Brasil. Ministério de Salud. Microcefalia: Ministério da Saúde divulga boletim epidemiológico. Brasilia: Ministério da Saúde, 2015. Available at: <http://bit.ly/1l6lhqu>
- 6.- Pan American Health. Neurological syndrome, congenital malformations, and Zika virus infection: implications for public health in the Americas. Epidemiological alert December 2015. Available at: <http://bit.ly/22Lhwsq>
- 7.- Brasil. Ministério da Saúde. Novos casos suspeitos de microcefalia são divulgados pelo Ministério da Saúde, [Internet]. Brasília: Ministério da Saúde, 2016. Available at: <http://bit.ly/1Kc2H6s>
- 8.- ASCOM Fiocruz-Paraná. Pesquisa da Fiocruz Paraná confirma transmissão intra-uterina do zika vírus. [Internet]. Paraná; 2016. Available at: <http://bit.ly/1OUiLMi>
- 9.- Brasil. Ministério da Saúde . PORTARIA Nº 1.813, DE 11 DE NOVEMBRO DE 2015 Declara Emergência em Saúde Pública de importância Nacional (ESPIN) por alteração do padrão de ocorrência de microcefalias no Brasil. Available at: <http://bit.ly/1SgfMSO>

10.- Pan American Health Organization. Increase of microcephaly in the northeast of Brazil. Epidemiological alert. November 17 2015. Available at: <http://bit.ly/1SlooYe>

11.- Pan American Health Organization. Zika virus infection: updated. Epidemiological alert. October 16, 2015. Available at: <http://bit.ly/1ND1SDU>

12.- Pan American Health Organization. Neurological syndrome, congenital malformations, and Zika virus infection: implications for public health in the Americas. Epidemiological Alert. January 17, 2016. Available at: <http://bit.ly/1WOmPCU>

13.- Pan American Health Organization. Zika virus (ZIKV) surveillance in the Americas: interim guidance for laboratory detection and diagnosis. 29th June 2015. Available at: <http://bit.ly/1S96GsO>

14.- World Health Organization, Regional Office of Western Pacific.. Zika virus, May 2015. Available at: <http://bit.ly/1HppSYM>

15.- Miller MW, Church CC Arrhenius thermodynamics and birth defects: chemical teratogen synergy. Untested, testable, and projected relevance. Birth Defects Res C Embryo Today. 2013 Mar;99(1):50-60. doi: 10.1002/bdrc.21025

16.- US. Food and Drug Administration. Acetaminophen Overdose and Liver Injury —Background and Options for Reducing Injury. Available at: <http://1.usa.gov/1tokboe>

17.- Royal College of Obstetricians and Gynaecologists. Obstetric Cholestasis. Green-top Guideline No. 43 April 2011. Available at: <http://bit.ly/1JA6S19>

18.- So M, Bozzo P, Inoue M, Einarson A. Safety of antihistamines during pregnancy and lactation. Can Fam Physician 2010; 56(5):427-429. Available at: <http://1.usa.gov/1RKd2OQ>

19.- European Centre for Disease Prevention and Control. Rapid risk assessment: Microcephaly in Brazil potentially linked to the Zika virus

epidemic – 24 November 2015. Stockholm: ECDC, 2015. Disponible en: <http://bit.ly/20pU7KM>

20.- Pan American Health Organization. Fescina RH, De Mucio B, Díaz Rossello JL, Martínez G, Serruya S, Durán P. Sexual and reproductive health: guides for the PHC focused continuum of care of women and newborns. 3 ed. Montevideo: CLAP/WR; 2011 (CLAP/WR. Scientific Publication, 1577-02) Available at: <http://bit.ly/1PQthUt>

21.- Bianchi DW, Crombleholme TM, D'Alton ME, Malone FD. Fetology, diagnosis and management of the fetal patient. 2nd ed. New York: Mc Graw Hill, 2010

22.- Leibovitz Z, Daniel-Spiegel E, Malinger G et al. Microcephaly at birth - the accuracy of three references for fetal head circumference. How can we improve prediction? Ultrasound Obstet Gynecol 2015 Oct 29. doi: 10.1002/uog.15801. [Epub ahead of print]

23.- US. Centers for Disease Control and Prevention. Zika Virus Transmission. Jun 1, 2015. Available at: <http://1.usa.gov/1OxSOUR>.