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INTERIM GUIDANCE

ISUOG Interim Guidance on ultrasound for Zika virus infection in pregnancy: information for healthcare professionals

In response to the World Health Organization (WHO) statements and international concerns regarding the Zika virus (ZIKV) outbreak, ISUOG is publishing the following guidance for ultrasound during pregnancy.

With the current uncertainty regarding many aspects of the diagnosis and clinical course of ZIKV infection in pregnancy, potentially valuable information may be obtained by ultrasound practitioners that may help in counseling pregnant women and further improve our understanding of the pathophysiology of ZIKV infection in pregnancy.

This statement is not intended to replace previously published interim guidance on evaluation and management of ZIKV-exposed pregnant women. It should therefore be considered in conjunction with other relevant advice from organizations such as:

WHO: http://www.who.int/emergencies/zika-virus/en/
Centers for Disease Control and Prevention (CDC): http://www.cdc.gov/zika/pregnancy/index.html
Pan American Health Organization (PAHO): http://www.paho.org
European Centre for Disease Prevention and Control (ECDC): http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/Pages/index.aspx
Public Health England: https://www.gov.uk/guidance/zika-virus

BACKGROUND

There is an outbreak of ZIKV infection in the Americas, Caribbean and South Pacific[1,2]. The infection is spread mainly by *Aedes* mosquitoes, although a small number of cases from sexual transmission have been reported[3]. The wide distribution of the mosquito, combined with the lack of immunity in the population, has led to rapid evolution of the outbreak.

Most cases of ZIKV infection are self-limiting and without sequelae, but there have been cases of Guillain–Barré disease post-infection. In addition, clusters of cases of brain anomalies and microcephaly in some areas with known ZIKV transmission have been reported. This increased number of children with microcephaly has led to a high level of concern among pregnant women living in or traveling to endemic areas. ZIKV can cross the placenta and has been detected using polymerase chain reaction (PCR) analysis of amniotic fluid of pregnancies affected with fetal structural brain abnormalities and microcephaly[4], and ZIKV has been isolated post-mortem from the brain of a fetus with microcephaly[5]. A causal relationship between *in-utero* exposure to ZIKV and microcephaly is now likely, though not yet fully established[6].

It should be remembered that, for fetal abnormalities to occur due to congenital infection, a number of steps are needed: maternal exposure; maternal infection; fetal infection; and fetal affection. How these steps progress in ZIKV infection is unknown: we do not know how many women exposed in pregnancy become infected, how many of those infected will transmit to the fetus, and what proportion of infected fetuses will suffer effects. It is also important to note that, although microcephaly has been observed, this may well represent the severe end of the spectrum of effects and the co-existence of other abnormalities, while unknown, is likely. The gestational age at which infection occurs is important in other congenital infections, such as cytomegalovirus and toxoplasmosis, and it is probable that ZIKV infection poses the greatest risk in early pregnancy, although effects throughout pregnancy cannot be excluded confidently[7].

As the situation is evolving rapidly, this guidance will be updated periodically.

DIAGNOSIS

National guidelines should be followed regarding testing. Expert opinion should be sought from national reference laboratories. In general, testing for ZIKV is possible in maternal serum by reverse transcription PCR (RT-PCR) or detection of ZIKV-specific IgM antibodies[8,9]. The limitation of RT-PCR testing is that it can detect ZIKV only during, or immediately following, acute infection. ZIKV IgM testing is problematic because of cross-reactivity with other Flaviviruses and some immunizations. This may lead to an unreliably high false-positive rate of ZIKV serological testing, but negative serology results may be of value in 'ruling out' past ZIKV infection. Expert interpretation of both is required and is beyond the scope of this guidance.

RECOMMENDED MANAGEMENT ALGORITHM

In pregnant women with ZIKV exposure and symptoms, positive Flavivirus serology or proven ZIKV infection, or in those with exposure and/or symptoms but who have not had positive serology results, referral for detailed ultrasound assessment is appropriate.

1. Accurate assignment of gestational age

Accurate estimation of gestational age (GA) is of the utmost importance in order to plot appropriately fetal growth, in particular head circumference (HC) growth. Therefore, a careful assessment of existing scan results should be undertaken.

- Fetal crown–rump length (CRL) measurement before 14 weeks is the most accurate method for GA assessment.
- If this is not available a careful history should be taken to establish the last menstrual period and its reliability, and compared with the first reliable ultrasound.
- The use of HC for GA estimation, especially in the third trimester, should be avoided.

2. Baseline ultrasound scan

A baseline ultrasound scan should be performed on referral. As a minimum this should involve the following.

In cases referred < 14 weeks:

- Measurement of fetal CRL, biparietal diameter (BPD) and HC.
- Assessment of fetal anatomy[10].

In cases referred ≥ 14 weeks:

- Fetal biometry, including BPD, HC, abdominal circumference (AC) and femur length (FL)[10,11].
- Assessment of fetal anatomy[11].
- Measurement of the lateral ventricles and transcerebellar diameter (TCD)[12].
- In addition, and until more knowledge is acquired, assessment for intracerebral findings associated with other congenital infections, including presence of calcifications, periventricular or intraventricular echogenicities and irregularly shaped lateral ventricles[13].

3. Subsequent ultrasound scans

It is not known if, or when, fetal signs occur following maternal ZIKV infection. Given the uncertainties around diagnosis, the ISUOG panel consensus is as follows:

- Careful assessment of the availability of resources should be undertaken, in order to prevent loss of important routine ultrasound examinations at population level for those women not exposed to ZIKV.
- On balance, ultrasound assessment as described above, should be performed every 4–6 weeks, if local resources permit. Given that interval growth is particularly relevant, an interval of 6 weeks is more likely to produce a robust diagnosis and reduce false-positive rates, but this needs to be balanced against later diagnosis.

4. Deviation from normal

If ultrasound assessment shows a fetal HC of 2 SD below the expected mean for gestational age, or a fetal brain abnormality (such as intracranial calcifications or ventriculomegaly), referral to a specialist center for detailed assessment, including neurosonography of the fetal brain, should be undertaken[12].

Most fetuses in which the only finding is a HC of 2 SD below the mean would be expected to represent the lower end of the normal population distribution. An interval scan in 2–3 weeks should be arranged[14,15].

Given the current uncertainty, existing evidence and experience from prenatal imaging findings in other infections should be taken into account; these include the presence of irregularly shaped ventricular margins, increased periventricular echogenicity with or without cystic lesions, intraventricular adhesions, calcifications, callosal or vermian dysgenesis, small TCD, enlarged cisterna magna and/or increased amount of cerebrospinal fluid around the brain[4,13].

In cases in which subsequent scans show a further decline in fetal HC growth, to below −3 SD, or in those with definitive coexistent brain abnormalities, further assessment should include the following:

- Discussion of the advantages and risks of an amniocentesis for ZIKV RT-PCR. Expert virology advice should be sought before any such procedure. The mother should be made aware that the sensitivity and specificity of this test for detecting congenital infection are unknown and that the likelihood of the fetus being affected is also unknown. However, in the case of a fetal brain abnormality on ultrasound and a positive ZIKV RT-PCR result, the likelihood of the two being associated is high.
- Consideration of performance of fetal brain magnetic resonance imaging, if available, which may detect abnormalities that are not visible on ultrasound.

Depending on local laws, pregnancy termination may be discussed, based on GA and severity of the findings. Uncertainties regarding the condition should be made clear.

5. Postnatal assessment

Standardized HC measurements should be undertaken and plotted on standards that take into account GA at birth and sex[16,17]. The use of a single cut-off regardless of GA is not recommended[18].

When there has been laboratory confirmation of maternal or fetal ZIKV infection[8]:

- Placental histopathological examination and ZIKV testing of placental tissue and umbilical cord blood should be considered.
- Babies should be followed up into childhood for signs of any adverse effects of congenital ZIKV infection.

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