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ISUOG Practice Guidelines: The Role of ultrasound in Congenital Infections

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Running Head: Congenital Infections

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Clinical Standards Committee

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Introduction

Ultrasound scanning plays a key role in the diagnosis and management of congenital infection. In some cases, the initial finding of abnormal ultrasound features may trigger maternal serological testing for these infections; in others, either infection screening or the mother's symptomatology may lead to focused ultrasound scans aiming to detect potential fetal sequelae. Once congenital infection is diagnosed, ultrasound can be used to help determine the prognosis for the fetus and to guide further investigation and management. This paper will examine the role of ultrasound in the diagnosis and management of congenital infections.

Scope

- Ultrasound signs suggestive of congenital infection
- The prognostic value of ultrasound findings in congenital infections
- Cytomegalovirus (CMV)
- Toxoplasma
- Parvovirus B19
- Rubella
- Varicella-Zoster virus (VZV; chickenpox)
- Zika virus

For each infection, we will cover the ultrasound signs, timing of infection in relation to the gestational age, diagnosis of maternal infection, diagnosis of fetal infection, and a brief outline of the management. This guideline does not address prevention or routine screening for congenital infections, as this can differ across countries. Therefore, clinicians should follow local guidelines on whether to offer screening or not, gestation at screening, method of screening, interpretation of the test and follow-up of those who are screen-positive or screen-negative.

Despite the fact that intrauterine herpes simplex virus (HSV) infection has been reported in the literature as case reports, it was not included in this guideline as the majority of neonatal HSV infections are acquired at birth as a consequence of direct fetal contact with the infected birth canal or through an ascending infection after premature rupture of the

amniotic membranes. Intrauterine transmission of HSV infection from mother to the fetus is rare; estimated to occur in only 5% of the cases secondary to hematogenous transplacental dissemination.

Identification and assessment of the evidence

The Cochrane Library and Cochrane Register of Controlled Trials were searched for relevant randomized controlled trials, systematic reviews and meta-analyses. A search of Medline from 1966 to 2019 was also carried out. The date of the last search was 15th May 2019. Relevant conference proceedings and abstracts were also searched. Databases were searched using the relevant MeSH terms including all sub-headings. This was combined with a keyword search using 'congenital, 'infection, 'pregnancy', 'ultrasound', 'cytomegalovirus', 'zika', 'toxoplasma', 'rubella', 'varicella-zoster virus', 'parvovirus' and 'abnormalities'. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections and clinical trial registries. The search was limited to the English language. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are annotated as 'good practice points.'

Ultrasound Signs Suggestive of Congenital Infection

Table 1 illustrates the ultrasound signs suggestive of congenital infection. The presence of any of these ultrasound signs is not diagnostic of congenital infection, merely suggestive, but should trigger testing for CMV, toxoplasma, rubella, VZV and zika virus infection. In cases with fetal hydrops or anaemia, testing for parvovirus should also be included.

Pregnant women who present with a non-vesicular rash and/or other signs or symptoms suggestive of systemic viral infection should be offered testing for rubella and parvovirus B19. Women who present with a facial rash (suggestive of 'slapped cheek' syndrome) should be offered testing for parvovirus B19. Those with a history of potential exposure to toxoplasma and presenting with general malaise suggestive of systemic infection should be offered testing for this infection. Travel history of the woman or her partner to countries known to have zika virus transmission should trigger testing for zika virus.

<u>Congenital infections</u>

If a fetus is infected, the earlier in gestation this happens, the more likely it is to be *affected*. The most common tests utilized for diagnosing these infections are enzyme-linked immunosorbent assay (ELISA) tests. Paired serology testing, ideally with one test from before the primary infection, is often helpful to diagnose and determine the timing of the infection in relation to the gestational age. The timing of appearance of virus-specific IgM and IgG antibodies between the first and the second samples is helpful to interpret the test results and diagnose and time the infection. Antibody avidity testing can also be helpful in this regard; the longer the time since the initial infection, the greater the level of avidity.

<u>Diagnosing infection in the fetus</u>

Once a maternal infection has been diagnosed by the appropriate serological testing (whether triggered by maternal symptoms, contact with another infected individual, or by the discovery of ultrasound abnormality), the possibility of fetal infection must be contemplated.

Definitive diagnosis of fetal infection is possible only by invasive testing, usually by obtaining amniotic fluid by amniocentesis, or occasional fetal cord blood sampling. As a rule, the amniotic fluid PCR testing will not be positive until 6 to 8 weeks after the initial maternal infection. Moreover, fetal urination is not well established until at least 18-20 weeks' gestation, so amniocentesis is likely to be negative before then as the virus is not yet passed in urine in adequate concentrations. This means that amniocentesis should be delayed until after 18-20 weeks' gestation and, ideally, more than 8 weeks after the initial maternal infection. There is retrospective evidence showing that the most significant risk factors for false-negative results are time interval <8 weeks and gestational age at amniocentesis <18 weeks [1].

It is important to note that the confirmation of fetal infection does not necessarily mean that the fetus will be *affected* by this pathogen. An infected fetus may never develop any structural abnormalities identifiable on ultrasound scan or postnatal imaging such as MRI scan. It is also important, however, to recognize that even fetuses that do not exhibit any imaging abnormalities may still suffer long-term sequelae, which may be difficult to predict. This should be considered in the long-term follow-up of such cases.

Cytomegalovirus

Cytomegalovirus (CMV), a member of the human herpesvirus family, is the most common viral cause of congenital infection, affecting 0.2 – 2.2% of all live births [2–4]. It is the leading non-genetic cause of sensorineural hearing loss (SNHL) and a major cause of neurological disability. Around 10-15% of neonates with congenital CMV will be symptomatic at birth, and up to 25% of children with congenital CMV infection have long-term impairments [5,6].

Epidemiology

CMV infection may be acquired for the first time during pregnancy (primary infection) or women may experience non-primary CMV infection, either by reactivation of prior CMV infection or by a new infection with a different strain of the virus. Antenatally, transmission of the virus to the fetus occurs via the placenta. Transmission is more likely following primary maternal infection in pregnancy than following non-primary infection [7]. Infants born to mothers with primary infection have a risk of congenital infection of the order of 30-40%[8].

Following non-primary CMV infection in pregnancy, the risk of congenital infection is in the order of 1-2% [4]. The risk of congenital infection appears to vary according to the time during gestation at which primary infection occurs, increasing from around 30% in the first trimester to 47% in the third trimester [9,10]. While the risk of viral transmission is lower in early pregnancy, the proportion of cases with a prenatal diagnosis of severe fetal infection is higher when infection occurs in the first compared with the third trimester of pregnancy [11,12]. Correspondingly, the long term consequences for the fetus are higher, with recent evidence suggesting that long term sequelae occur only after first trimester infection.

The majority of women who acquire CMV infection for the first time (primary infection) will remain asymptomatic [13]. However, a minority experience symptoms similar to those of infectious mononucleosis (glandular fever), including fever, malaise, myalgia, cervical lymphadenopathy

and, less commonly, hepatitis and pneumonia, but few suffer long-term sequelae. Just as with other herpes viruses, CMV can remain dormant lifelong at particular sites, primarily in the salivary glands, but the virus can be reactivated at any time, including during pregnancy.

What are the diagnostic criteria of maternal CMV infection?

Recommendations

- The diagnosis of primary CMV infection in pregnancy can be made by one of the following findings: (i) the appearance of CMV-specific IgG in a woman who was previously seronegative, or (ii) the detection of CMV IgM antibody with low IgG avidity. *Grade: B*
- Non-primary maternal infection cannot be excluded using serological tests. *Grade: C*

The clinical features of congenital CMV at birth include infants born small for gestational age, microcephaly, jaundice, petechiae or purpura, 'blueberry muffin' rash indicating extramedullary haematopoiesis, and hepatosplenomegaly. Since routine antenatal CMV screening does not meet several of the criteria for an effective screening test, not least the fact that until now there has been no effective treatment in pregnancy, routine prenatal screening is not recommended in most countries [14,15]. Consequently, serological testing for CMV is offered only to women who have developed influenza-like symptoms, or symptoms of glandular fever (with negative test results for Epstein-Barr virus) or of hepatitis (with negative test results for hepatitis A, B and C) during pregnancy, or in whom routine ultrasound detects fetal abnormalities suggestive of possible CMV infection, such as ventriculomegaly, microcephaly, calcifications, intraventricular synechiae, intracranial hemorrhage, periventricular cysts, cerebellar hypoplasia, cortical abnormalities, echogenic bowel, small for gestational age, pericardial effusion, ascites or fetal hydrops [16,17]. The frequency of fetal ultrasound abnormalities in cases with congenital CMV infection is shown in Table 2 [16].

For other viral infections, such as rubella, the presence of IgM is often diagnostic of recent primary infection. However, this is not the case for CMV [18] for several reasons:

- IgM may persist for many months after the primary CMV infection
- IgM may be detected during a secondary infection
- There may be cross-reactivity with IgM due to another viral infection, e.g. Epstein-Barr virus
- IgM may be detected as a result of non-specific polyclonal stimulation of the immune system

Therefore, CMV-specific IgG testing should be performed in parallel with IgM testing, along with IgG avidity testing for seropositive women, to indicate the timing of the infection (i.e. before or during pregnancy). In general, a high avidity index (>60%) is highly suggestive of past (more than 3 months) or secondary infection, while a low avidity index (<30%) is highly suggestive of a recent primary infection (i.e. within the past 3 months) [19].

Diagnosis of non-primary CMV infection can be difficult. A rise in IgG levels does not confirm secondary infection as this may be due to non-specific polyclonal stimulation of the immune system. In practice, therefore, the only way of confirming secondary CMV infection and transmission to the infant is by CMV PCR testing of amniotic fluid.

The diagnosis of *primary* CMV infection in pregnancy can be made by one of the following

findings:
1. The appearance of CMV-specific IgG in a woman who was previously seronegative.
2. The detection of CMV IgM antibody with low IgG avidity.

What are the diagnostic criteria of fetal CMV infection?

Recommendation

- Fetal infection should be diagnosed by PCR detection of CMV DNA in the amniotic fluid. Amniocentesis should be delayed until at least 8 weeks after maternal infection and after 20 gestational weeks — *Grade: B*
- The most significant risk factors for false-negative results are time interval between infection and amniocentesis <8 weeks and gestational age at amniocentesis <17 weeks — *Grade:C*

The diagnosis of fetal infection is made by identification of the virus or viral genome (DNA) in the amniotic fluid following amniocentesis using PCR. The timing of amniocentesis is very important; the appearance of the virus in the amniotic fluid is dependent on the delay of the virus in crossing the placenta and on the excretion of the virus in fetal urine. It should be performed, therefore, at least 8 weeks after maternal infection and after 20 weeks of gestation[1,20–22], when fetal urination is well-established. There is retrospective data showing that the sensitivity of amniotic fluid PCR may be similar at 17 or 20 weeks, provided that there is a time interval of at least eight weeks between maternal infection and amniocentesis. The two most significant risk factors for a false negative result are time anterval <8 weeks and amniocentesis before 17 weeks [1].

What are the prenatal prognostic indicators in congenital CMV infection?

Following prenatal diagnosis of fetal CMV infection, the main aim is to predict the risk of symptomatic neonatal infection. In the medical literature, the risk of a 'poor outcome' as assessed prenatally is probably over-estimated. This is because 'poor outcome' is usually defined as a combination of those fetuses undergoing termination in whom post-mortem examination confirms significant signs of CMV infection together with infants born with symptomatic congenital CMV infection. However, finding at post-mortem examination features of CMV, such as cytomegalic inclusions in the kidneys and isolated periventricular calcifications, is probably not associated with a high risk of symptomatic neonatal infection. Therefore, the estimates of poor outcome as defined in the literature should be viewed with a degree of caution. It is also important to point out that what is being predicted, often it is a symptomatic infant at birth or changes on brain MRI. However, we should acknowledge that late onset SNHL or less severe neurodevelopmental adverse sequale may become evident only later – thus highlighting the importance of pediatric and hearing follow-up of all infected infants.

Accurate prenatal prediction of poor prognosis for affected infants has proved challenging; estimates are based largely on three factors: 1. Timing of the infection; 2. Presence and type of fetal abnormalities; 3. Laboratory parameters.

i. Gestational age at maternal infection

Recommendations

- Women should be informed that an indicative likelihood of vertical transmission is 15% after primary maternal infection at the preconception period, 30% at the periconceptional period and first trimester, 35% at the second and 65% at the third trimester *Grade: C*
- Women should be informed that, based on limited data, an indicative likelihood of severe symptoms at birth in an infected fetus is 70% after primary maternal infection in the periconceptional period, 20% after primary maternal infection in the first trimester, 5% in the second and probably negligible in the preconception period and third trimester. *Grade: C*

It appears that in common with other viral infections, the risk of vertical transmission increases with gestation. The association between the timing of infection and *severity* of fetal/neonatal outcome is less well defined.

Although Stagno at el [11] did not find a difference in vertical transmission rates in any of the trimesters, more recent studies strongly suggest a higher rate of transmission with advancing gestational age. For example, one study [23] found a 75% rate of transmission following primary infection after 25 weeks' gestation. Bodeus at el [24] followed 123 women who developed a primary CMV infection during pregnancy. The overall rate of transmission in the study population was 57.5%. They found a statistically significant difference in the rate of vertical transmission between the first trimester and the third trimester (36% versus 77.6%; $p<0.001$); the risk of transmission during the second trimester was 44.9%.

Another study [25] assessed the risk of vertical transmission following primary maternal infection at the pre-conception stage (between 8 and 2 weeks before the start of the LMP), peri-conception (between 1 week before and 5 weeks after the LMP) and later in pregnancy (between 6 and 20 weeks' gestation, and between 20 and 38 weeks' gestation). They found no cases of congenital infection in the pre-conception group while congenital infection occurred in 45% of cases in the peri-conception group. When the primary infection occurred between 6 and 20 weeks' gestation, the transmission rate was 30%, and between 20 and 38 weeks' gestation it was 58%. Revello et al [21] found that 9% of neonates were CMV infected but had no clinical features at birth following pre-conceptional maternal infection and 31% in the peri-conception group, where a virological outcome was known. In another study, the same authors [26] found that following pre-conceptional infection (2-18 weeks before the LMP), 8% of the neonates examined at birth were CMV infected but had no clinical features at birth. A more recent study [27] examined peri-conceptional primary CMV infection and found a vertical transmission rate of 25%.

The association between the gestation of primary maternal CMV infection and neonatal outcome is less well defined mainly because, in the absence of a systematic antenatal serological screening program and given that 90% of primary infection is asymptomatic, the timing of maternal infection is often imprecise. Nevertheless, there is growing evidence that, in common with other viral infections in pregnancy, infection earlier in pregnancy is associated with a greater risk of more severe harm to the fetus/neonate. Pass at el [12] identified neonates with congenital CMV infection, then retrospectively tested stored maternal serum collected during pregnancy. They tested these samples for IgG and IgM antibody levels and used the results to classify

primary maternal infection as first trimester (less than 13 weeks' gestation) or later. They found SNHL in 24% of the children in the first-trimester group, compared to 2.5% in the later group (relative risk [RR] 9.6). They found any CNS disability (hearing loss, mental handicap, cerebral palsy, seizures or chorio-retinitis) in 32% of first trimester cases compared with 15% in the later group (RR 2.2). None of the late infection group had more than 1 disability whereas 12% of the first-trimester group did (p=0.04).

Liesnard at el [20] had similar findings. They dated the fetal infection based on amniotic fluid or fetal blood testing in 55 cases of congenital CMV from 237 pregnancies that underwent prenatal evaluation. They found that 26% of fetuses infected before 20 weeks of gestation had severe disease compared with only 6% of fetuses infected after 20 weeks.

Recent evidence from more than 350 pregnancies with maternal CMV seroconversion suggests that mostly first-trimester infection is likely to be associated with severe CMV infection [28,29].

ii. Presence of fetal abnormalities

Recommendations

- Women should be informed that normal brain findings on ultrasound and fetal MRI are associated with low risk of infant disability. However, this is not indicative of hearing outcomes. *Grade: C*
- Women should be informed that ultrasound abnormalities can appear 12 weeks or longer after maternal infection, therefore detailed ultrasound follow-up for the remainder of the pregnancy is indicated *Grade: C*

In the absence of a routine antenatal screening program for CMV, the most common circumstance in which CMV is diagnosed prenatally is following the discovery of an abnormal ultrasonographic finding suggestive of possible CMV infection at a routine ultrasound scan. This will lead to serological testing of the mother and/or amniocentesis with PCR. As a result of this non-systematic mode of discovery, severe ultrasound abnormalities are described more often than subtle findings. Nevertheless, a retrospective study of women with maternal primary infection in the index pregnancy found that, once the diagnosis of fetal infection had been made by PCR confirmation of CMV in the amniotic fluid, ultrasound became more sensitive for the detection of more subtle abnormalities associated with the fetal infection [16].

Ultrasound findings can be categorized as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormality (Figure 1). The ultrasonographic cranial features of CMV infection vary but include ventriculomegaly, microcephaly, calcifications, increased periventricular echogenicity or halo, periventricular pseudocysts, intraventricular synechiae, abnormalities of cortical development and of the cerebellum and posterior fossa, or cerebral hemorrhage [30] (Figure 1). Extracranial fetal abnormalities also vary but include splenomegaly, hepatomegaly, hyperechogenic bowel, isolated pleural or pericardial effusion, ascites, fetal hydrops and cardiomegaly.

It is important to be aware of the lag time between maternal infection and fetal infection, and then from fetal infection until the appearance of sonographically identifiable fetal abnormalities. The placenta appears to act as a reservoir for, and a barrier to, infection, explaining why not all

maternal primary infection (and maternal viremia) results in fetal infection. Some studies have observed a thickened placenta with a heterogeneous appearance and calcification, suggesting placentitis, before the appearance of fetal infection [31]. The time interval between primary maternal infection and the appearance of fetal ultrasonographic abnormalities varies considerably in the cases reported in the literature. In a series of 189 cases of primary infection with known outcomes, this interval appeared to be around 12 weeks (following maternal infection at 14 weeks' gestation) [22]. However, longer intervals have been reported; Nigro et al. [32] described a case where primary maternal infection occurred at six weeks' gestation, but the ultrasound abnormalities (intraventricular hemorrhage) did not appear until 20 weeks' gestation. Another case report of infection in an HIV positive woman at six weeks' gestation found that the ultrasound abnormalities were not apparent until as late as 36 weeks' gestation. The implications of these findings for clinical practice are that, even if fetal infection occurs early in pregnancy, detailed ultrasound follow-up for the remainder of the pregnancy is indicated [33].

It appears that the main sonographic prognostic indicator is fetal cerebral abnormalities. In a small retrospective study, Farkas et al. found that if the antenatal ultrasound examination of the fetal brain was normal, then normal early neuropsychological outcome was likely [34]. Such conclusions led to the evaluation of fetal cerebral magnetic resonance imaging (MRI) for further assessment of the fetal brain. MRI using both T1 and T2 sequences can be used to help to define the timing and consequences of fetal infection.

Ultrasound and MRI should be considered as complementary imaging modalities for the investigation of the fetal brain [35]; when both are performed in the third trimester in a fetus known to be infected with CMV, they have a 95% sensitivity for the identification of related CNS lesions. When both ultrasound and MRI of the fetal brain are normal prenatally, the neonatal outcome is generally good, and the same may be true for a normal ultrasound with only subtle findings on MRI [36]. Similarly, a recent study found that subtle findings on prenatal MRI were associated with a favorable prognosis; MRI had a high negative predictive value for SNHL and neurological impairment, and that this was equally predictive at either 27 or 33 weeks of gestation [37].
The combined predictive value of a normal ultrasound and MRI evaluation to predict an asymptomatic neonate, in fetuses known to be infected with a positive amniocentesis and when imaging was performed up to the third trimester, after 30 weeks, is at best 95%. Fetal laboratory findings may bridge this 5% gap. It is important to point out that this is not indicative of hearing outcomes, i.e. normal antenetal ultrasound and MRI does not rule out the risk of hearing loss in these fetuses.

iii. Laboratory parameters

Recommendations

- Although the median viral load in the amniotic fluid may be higher in symptomatic than in asymptomatic fetuses, its overlap between the two groups and its dependence on technical and temporal factors, reduce its prognostic value — *Grade:B*
- Although fetal blood markers such as platelet count, beta-2 microglobulin and CMV IgM have been associated with prognosis, the added value of fetal blood sampling in the prognostic workup of these women is not certain. — *GPP*

Several studies [38–40] have examined the relationship between the viral load in the amniotic fluid and the likelihood of the fetus being symptomatic. All of these studies found that the median viral

load was higher in the amniotic fluid of symptomatic fetuses than in that of asymptomatic fetuses; however, this difference was statistically significant in only one study [38]. Furthermore, some fetuses with high amniotic fluid viral loads were born asymptomatic, while others with low amniotic fluid viral load had severe ultrasound abnormalities [39]. Some of these differences may be explained by the methodology used or by the time interval between seroconversion and amniocentesis, as there is evidence that the amniotic fluid viral load changes with time elapsed since seroconversion [38,40].

Studies of CMV genotypes have not found a good correlation with the fetal outcome [39,41,42].

Prenatal fetal blood sampling has also been investigated for possible prognostic indicators, looking at both virus-specific markers as well as non-specific fetal blood parameters. It has been shown that the mean viral load in the blood of infected neonates is significantly higher in symptomatic neonates compared with asymptomatic ones (p=0.02), and this difference was more marked when considering only infants with severe symptomatic congenital CMV infection [43]. However, there is significant overlap between symptomatic and asymptomatic neonates, so setting a discriminatory cut-off is not feasible [44]. Revello et al [45] found that antigenemia, viremia and DNA load were higher in the blood of neonates with ultrasound abnormalities compared to those without, but the difference was statistically significant only for antigenemia.

Several authors have investigated various non-specific neonatal blood parameters, including thrombocytopenia (platelet count <100,000/mm^3), alanine aminotransferase (>80 IU/ml) and direct bilirubin (>4 mg/dl). Rivera et al. [46] found that all of these were associated with symptoms at birth, with odds ratios of 2.4, 7.1 and 2.8, respectively. Another study pointed to the importance of thrombocytopenia; it found that among symptomatic CMV-infected neonates with a normal cranial computed tomographic (CT) scan, 56% had thrombocytopenia vs. 86% of those with an abnormal cranial CT [47].

In summary, therefore, the literature suggests that the platelet count in a fetal blood sample is an independent prognostic indicator of neonatal outcome and in certain circumstances could justify the risk of fetal loss (in the order of 1-2%[48]) associated with fetal blood sampling. However, there are controversial views among clinicians, as some argue that 1-2% risk of fetal loss does not justify fetal blood sampling for the platelet count which does not give us sufficiently certain information upon which to base decisions. In general, fetal blood sampling may be considered of greatest value in the 'intermediate' prognostic group, i.e. in a fetus that has non-cerebral ultrasound abnormalities or in a pregnant woman who requires as much information as possible on prognosis to decide on her management options. At the time of prenatal diagnosis of congenital CMV infection, the negative predictive value using ultrasound findings for symptomatic infection at birth or termination of pregnancy is estimated to be 93% [49]. The combined negative predictive values of ultrasound and viral load in the amniotic fluid and that of ultrasound and fetal blood parameters are 95% and 100%, respectively. In fetuses presenting with non-severe ultrasound features, the positive predictive values of ultrasound alone and in combination with amniotic fluid viral load or with fetal blood parameters are 60%, 78%, and 79%, respectively [49]. This questions the additive value of the fetal blood markers obtained via cordocentesis above and beyond the amniotic fluid markers already obtained at the time of amniocentesis used for prenatal diagnosis [49].

Overview of prognostic categorization and challenges

Overall, infected fetuses may be classified into one of three prognostic categories [50]:

1. **Asymptomatic fetuses**: defined as those with no ultrasound abnormalities, normal cerebral MRI and normal biological parameters, in particular platelet count in fetal blood. The prognosis is generally good for these fetuses but with a residual risk of hearing loss.
2. **Mild or moderately symptomatic fetuses**: defined as those with isolated biological abnormalities (on fetal blood sampling), either without brain abnormalities on ultrasound or with isolated ultrasound abnormalities, such as hyperechogenic bowel, mild ventriculomegaly or isolated calcifications. In this group the prognosis is uncertain, and further follow-up (with ultrasound and possibly MRI) may help to refine the prognosis. Therapeutic options, such as antiviral therapy, are being evaluated, but their use is still limited to the research setting. The option of termination of pregnancy should also be discussed.
3. **Severely symptomatic fetuses**: defined as those with severe cerebral ultrasound abnormalities (e.g. microcephaly, ventriculomegaly, white matter abnormalities and cavitations, intracerebral hemorrhage, delayed cortical development) associated with thrombocytopenia. The prognosis for this group is poor, and counseling regarding the option of termination of pregnancy should take place.

It can be seen, therefore, that even taking all of these factors into account, the accurate prenatal prognosis of fetal CMV infection is challenging. There is a need for new and better prognostic tests for fetuses with congenital CMV. A recent study [51] performed peptidome analysis in the amniotic fluid of 13 symptomatic and 13 asymptomatic neonates, and found that a panel of 34 peptides had 89% sensitivity, 75% specificity and an area under the curve (AUC) of 0.90 to differentiate the nine severely symptomatic from the 12 asymptomatic neonates. This analysis may represent a useful prognostic indicator for the future [51].

What is the recommended management of maternal and fetal CMV infection?

Recommendations	*GPP*
• Due to the lack of randomized controlled trials, high-dose valaciclovir for congenital CMV infection should only be given in the context of research • Based on the results of one randomized controlled trial, administration of CMV-specific hyperimmune globulin (HIG) for congenital CMV infection is not recommended as part of clinical care and should only be given in the context of research	*Grade:B*

The antenatal diagnosis of CMV infection is challenging, and options for prevention and treatment are limited. In general, the options for congenital CMV infection are either conservative management, in other words a continuation of the pregnancy with regular monitoring, or termination of pregnancy. More recently, medical therapies aimed at reducing the risk of transmission, and likelihood and/or severity of neonatal infection, have been investigated, including antiviral drugs and CMV hyperimmune globulin (HIG) [52–54].

Two studies have shown promise for the use of valaciclovir in pregnancies with CMV-infected fetuses, but a randomized controlled trial is needed to confirm whether this antiviral should be

recommended routinely to reduce the risk of symptomatic congenital CMV disease [52,53]. High-dose valaciclovir was given for a median of 89 days to pregnant women carrying a moderately-infected fetus, presenting with non-severe ultrasound features (extracerebral ultrasound abnormalities and/or mild ultrasound brain abnormalities; see Table 3). Valaciclovir was associated with a significantly greater proportion of neonates born asymptomatic (82%) compared with a historical cohort (43%). This study also provided reassuring safety data for the use of valaciclovir in pregnancy: maternal clinical and laboratory tolerances to this high-dose regimen were excellent, and no adverse neonatal effects were observed.

Nigro et al. reported that CMV HIG therapy was associated with a significantly lower risk of congenital CMV infection, especially symptomatic infection [54]. Recently, a prospective observational study has reported that, after a primary maternal CMV infection in the first trimester, biweekly HIG administration at a dose of 200IU/kg prevented maternal-fetal transmission up to 20 weeks' gestation [55]. Unfortunately, the potential efficacy of HIG was not borne out in a phase-II randomized, placebo-controlled, double-blind study [56]. This study found no significant improvement in the risk of transmission, the levels of virus-specific antibodies, T-cell mediated immune response, viral DNA in the blood or clinical outcome at birth. Given these conflicting findings, HIG is currently not routinely recommended for the treatment of women with primary CMV infection in pregnancy. A trial assessing HIG in pregnancy was expected to finish in 2018 [57]. However, this study was stopped for futility.

A proposal for the management of CMV fetal infection is presented in Figure 2.[35] There is currently no licensed vaccine for CMV. An alternative strategy to reduce the risk of infection is behavior modification aimed at minimizing direct contact with saliva or urine of young children who may be excreting CMV in these fluids. Simple hygiene-based measures reduce the risk of CMV acquisition include avoiding sharing utensils, drinks or food with young children, not kissing young children directly on the lips and handwashing after contact with urine or saliva.

Congenital CMV should be confirmed at birth following an antenatal diagnosis of maternal infection, even where a diagnosis of fetal infection has been made by invasive sampling. Infants should have a urine sample or saliva swab tested for CMV PCR as soon as possible after birth and it is important to collect samples within three weeks of birth to confirm congenital rather than postnatal acquisition of CMV.

Toxoplasma

It is currently estimated that about 170 infants each year are born with congenital toxoplasmosis in the United States and has significantly fallen from what was reported before 1999 [58]. Similarly, the incidence in Europe has fallen in recent years due to improvements in levels of hygiene and increased knowledge and avoidance of foods and cat litter, particularly during pregnancy.
Over the 5 years between 2008 and 2012, 33 cases of congenital toxoplasmosis were identified through enhanced surveillance in England and Wales [59].

Toxoplasma gondii is a parasitic infection acquired by the ingestion of Toxoplasma tissue cysts [60]. These cysts may be found in meat, so pregnant women should ensure that any meat they eat is cooked well and they should avoid processed meat. The infectious oocysts are secreted by cats and can contaminate soil, so pregnant women should ensure that salads/vegetables are thoroughly washed and should take care to wash their hands, particularly before they eat, when

they have handled cats [61].

In the UK, only 10% of women of childbearing age are immune to toxoplasma and the incidence of maternal infection is around 2-5 per 1000 [62,63]. The primary maternal infection is asymptomatic in around two-thirds of women; the remainder have a mild coryzal illness with malaise, low-grade fever, headache and lymphadenopathy.

The overall risk of congenital toxoplasmosis following maternal infection ranges from 20% to 50% without treatment [64,65]. As with most viral infections in pregnancy, the risk of fetal infection increases with gestational age (less than 1% before 4 weeks, 4 to 15% at 13 weeks, greater than 60% at 36 weeks) [64,66]. Again, however, the earlier the gestation of infection, the greater the risk that the fetus will be affected (Table 4) [64].

The main sequelae of congenital toxoplasma infection are in the central nervous system and eyes, typically microcephaly, hydrocephalus, ventriculomegaly and chorioretinitis [67,68]. These may lead to developmental delay, epilepsy and blindness. Hepatosplenomegaly, anemia, rash, jaundice and pneumonitis may also occur [67,68]. Even though most infected infants do not have clinical signs of infection at birth, up to 90% will develop sequelae later in life [69–71].

What are the diagnostic criteria of maternal toxoplasmosis infection?

Recommendations

• In case of positive or equivocal IgM with a negative IgG, a new specimen for IgM and IgG should be obtained within two weeks. If the results remain unchanged, the IgM result is probably a false positive	*Grade:C*
• In the case of equivocal result for one antibody and positive of the other, a new specimen should be obtained within two weeks. If the results remain unchanged, both specimens should be sent to a reference laboratory.	*GPP*
• Women should be informed that a high IgG avidity result within the first 12-16 weeks of pregnancy (depending on the kit used) essentially rules out maternal infection during the index pregnancy	*Grade:C*
• However, physicians should be aware that spiramycin treatment can delay maturation of IgG antibodies and therefore result in lower avidity titers than in untreated women.	*Grade:B*
• An experienced reference laboratory should be consulted in any case of inconclusive serology results.	*GPP*

As with most infections, diagnosis is based on testing of maternal serum for IgG and IgM, and avidity testing can be useful to help to determine the timing of infection (Health Protection Agency, 2006). IgM is the first antibody to increase, reaching its highest level at about one month after infection and remaining relatively stable for about one more month before starting to decrease. IgG reaches its maximum level by about three months and, in the absence of treatment, only shows a mild decrease after this point [72].

IgM testing may not be that helpful for timing the infection; it usually appears within two weeks of exposure but can persist for years [70,73]. It is also notable that serologic assays for toxoplasmosis

are not well-standardized and have high rates of false-positive and false-negative test results [73,74]. Therefore, the tests should be performed in an experienced reference toxoplasmosis laboratory in which specific confirmatory tests, such as the Sabin–Feldman dye test or indirect fluorescent antibody test, are performed [70,73–75]. This is the case particularly for pregnant women with positive or equivocal IgM test results [75,76]. IgG will normally be detectable two weeks after exposure; the change in level at repeated testing (usually after two weeks) may help to determine the timing of infection.

The combination of negative IgM and negative IgG test results indicates either the absence of infection or a recent acute infection without enough time for seroconversion. The combination of negative IgM and positive IgG test results indicates remote infection and no risk of fetal transmission in an immunocompetent woman [73–75]. The combination of positive IgM and positive IgG test results indicates that the pregnant mother has had either a recent infection or a false-positive IgM result. If acute infection is a possibility, serologic testing should be repeated in 2–3 weeks to look for an increase in IgG antibodies consistent with recent infection [73–75]. Table 5 demonstrates the interpretation of the results of serological tests for toxoplasmosis performed at clinical (non-reference) laboratories [76].

As with other viral infections, IgG avidity testing may be helpful [77]; in general, high avidity is associated with primary infection occurring more than 4-5 months previously (depending on the test method used), while low avidity usually indicates infection within the previous 4-5 months [74,78–80]. However, in the case of toxoplasma, spiramycin treatment can delay the maturation of IgG antibodies [81], and avidity tends to be lower than expected in treated women [82,83].

The interpretation of toxoplasma test results may be challenging, and a specialist microbiologist should be consulted.

What are the diagnostic criteria of fetal toxoplasmosis infection?

Recommendations

- Fetal infection should be by detection of toxoplasma DNA in the amniotic fluid. Amniocentesis should be delayed at least four weeks after maternal infection and preformed after 18 gestational weeks *Grade:B*
- Women should be informed that the sensitivity of current molecular methods in detecting Toxoplasma DNA in the amniotic fluid is up to 90%; false-negative results can occur when the DNA concentration is low. *Grade:B*

Fetal infection can be diagnosed by identification of toxoplasma DNA (polymerase chain reaction) in the amniotic fluid (obtained by amniocentesis) [84]. Again, this should be delayed until at least four weeks after maternal infection and should be performed after 18 weeks' gestation, when fetal urine production is well established [76,85,86].
The sensitivity of amniocentesis using current PCR assays is up to 90% [87]. The false-negative results can be attributed to low levels of Toxoplasma DNA in the amniotic fluid [87,88]. However, these cases may have a better prognosis, as low titers of DNA were associated with less severe manifestations in the infant[87,88].

Ultrasound signs suggestive of fetal infection are commonly non-specific and include ventriculomegaly, intracranial bleeding, intracranial calcifications, microcephaly, ascites, hepatosplenomegaly, intrauterine growth restriction and hydrops (Figure 3 shows ultrasound/MRI images of affected fetuses). Limited evidence indicates that the combination of cerebral echogenic lesions and ventriculomegaly is associated with adverse prognosis (chorioretinitis with or without developmental delay) [89], whereas the prognosis of echogenic lesions with normal ventricles appears better (normal neurodevelopment in 4 of 5 cases) [90].

What is the recommended management of maternal and fetal toxoplasmosis infection?

Recommendations

• Spiramycin 1g tablet three times daily should be used for preventing vertical transmission after maternal toxoplasma infection during pregnancy	*Grade:C*
• Spiramycin treatment should be initiated within three weeks from maternal seroconversion	*Grade:B*
• If vertical transmission is confirmed, fetal infection should be treated by spiramycin only for one week, followed by pyrimethamine 50 mg once daily plus sulfadiazine 1 g three times a day plus folinic acid 50 mg weekly for one week	*Grade:C* *Grade:C*
• The combination of pyrimethamine, sulfadiazine and folinic acid may be more effective than spiramycin in preventing vertical transmission, but more data is needed before it can be adopted in clinical practice	*GPP*
• Ultrasound follow-up should include 4-weekly examinations of the fetus, focusing on brain, ocular and growth assessment	*Grade:B*
• Women should be informed that, even when fetal imaging studies are normal, there is a risk of approximately 30% for long-term sequelae, especially chorioretinitis which occasionally causes vision loss.	

When maternal toxoplasma infection occurs before 18 weeks' gestation, treatment with spiramycin should be commenced without delay until amniocentesis after 18 weeks' gestation. The most common dosing regimen is spiramycin 1 g orally three times a day. The earlier after primary maternal infection spiramycin is started, the more effective it is likely to be in reducing the risk of fetal infection. Nonetheless, there is still no evidence that prenatal treatment can significantly decrease the risk of clinical manifestations (1.11, 95% CI 0.61-2.02) [91]. It is noteworthy that, while increasing gestational age at seroconversion was associated with decreased risk of cerebral lesions, it does not affect the rate of ocular lesions [92]. Recently, the combination of pyrimethamine (50 mg/d PO) *plus* sulfadiazine (1 g tid PO) *plus* folinic acid (50 mg once a week) was compared to spiramycin (1 g tid PO) in a randomized controlled trial in the context of prevention of vertical transmission. It was found that the transmission rate was 18.5% in the pyrimethamine + sulfadiazine + folinic acid group, vs. 30% in the spiramycin group. The rate of cerebral anomalies was 0/73 in the former group, vs. 6/70 (8.5%) in the spiramycin group. Moreover, there appeared to be a three-weeks' window of opportunity for the initiation of treatment after maternal seroconversion. Two women in the pyrimethamine + sulfadiazine group developed severe rash that required hospitalization [93]. Since sulfadiazine can precipitate a hemolytic crisis in individuals with glucose 6-phosphate dehydrogenase (G6PDH) deficiency, G6PDH testing should be considered before the initiation of treatment.

After 18 weeks' gestation, it is still worth performing amniocentesis to confirm or exclude fetal infection. This is because, if fetal infection is confirmed by amniocentesis, the treatment regimen will be changed to spiramycin only for one week, followed by pyrimethamine 50 mg once daily plus sulfadiazine 1 g three times a day plus folinic acid 50 mg weekly for one week [85,86].

Postnatal treatment of newborns with symptomatic congenital toxoplasmosis consists of pyrimethamine, sulfadiazine, and folinic acid for one year [58].

It should be borne in mind that a negative amniocentesis does have a false negative rate, so even in this situation, serial ultrasound follow-up of the fetus is indicated. Ultrasound may identify the following features suggestive of congenital toxoplasma: microcephaly, hydrocephalus, ventriculomegaly, cerebral calcifications, cataracts, ascites. When ultrasound of the brain is normal, consideration should be given to fetal MRI as it has greater sensitivity for detecting subtle brain abnormalities. When the fetal ultrasound is normal, and particularly when the fetal MRI is also normal, the risk of significant neonatal sequelae is low, but parents should be counseled that even in this situation there remains a residual risk (approximately 30%) of significant sequelae, especially ocular [69–71].

Human Parvovirus B19

Recommendations

- Given the potential for long-term neurodevelopmental sequelae, cerebral imaging should be considered for fetuses who had hydrops or severe anemia *Grade:C*

Parvovirus B19 is a single-stranded DNA, non-enveloped virus from the family *Parvoviridae*, and the only member of the family that can cause human disease. Also known as fifth disease, it is such a common childhood viral infection that approximately 60-75% of pregnant women are immune [94,95]. Children who get this infection exhibit a characteristic facial rash and fever, when the condition is known as 'slapped cheek syndrome'. This will often run in epidemics through schools, especially during late winter and spring. It is spread by respiratory droplets from infected people, by blood or blood product transfusion or by transplacental passage [96]. The incidence of acute Parvovirus B19 infection in pregnancy is 1-2% [95]. Cases are often asymptomatic, although prodromal symptoms may be present after the incubation period of 4-14 days from exposure. In some cases, the more definable symptoms of rash (erythema infectiosum) and arthralgia are present seven days after the prodromal illness. The incubation period is 5 to 7 days following exposure; women remain infectious for 3 to 10 days post-exposure or until the rash appears.

The most common trigger for maternal testing for parvovirus B19 in pregnancy is a report of recent exposure; it can also result from an incidental finding of fetal hydrops (Figure 4) on ultrasound.

When a mother contracts infection, the risk of vertical transmission to the fetus ranges from 25% to 32% [97,98]. The main receptor for parvovirus B19 is globoside, a blood group P antigen, which is primarily found in erythroid precursors [99], but also in other tissues, including the myocardium and the first-trimester placenta [100]. Parvovirus B19 causes fetal anemia by inhibiting erythropoiesis, thus leading to the aplastic crisis. In healthy adults, this crisis is well tolerated, with minimal

anemia. However, compared with adults, the fetus has a greater demand for red blood cells and a larger red cell mass with associated rapid cell turnover. This renders the fetus particularly vulnerable to any insult to erythropoiesis, and profound anemia may result from infection with Parvovirus B19. In the fetus, the virus mainly affects the bone marrow but can also affect areas of extra-medullary hematopoiesis such as liver or spleen. The fetal anemia, as well as associated hepatitis, hypoalbuminemia and myocarditis, can lead to cardiac failure and subsequent hydrops fetalis [101]. Intrauterine red blood cell transfusion can be used to treat fetal hydrops caused by Parvovirus B19. Table 6 lists the reported ultrasound abnormalities in fetuses infected by Parvovirus B19 [102–105].

When a fetus is infected, there is no evidence that parvovirus is teratogenic but, as mentioned above, it can lead to fetal anemia. The risk of fetal hydrops is low (4-13%), but when it occurs, it carries a 50% risk of intrauterine fetal death [98,102,106]. Hydrops occurs at a median of three weeks after the primary maternal infection, and 95% of the cases develop by the eighth week after maternal infection [106]. Spontaneous resolution has been reported between 1 to 7 weeks after the diagnosis [107]. It is worth noting that thrombocytopenia has been reported in more than 95% of hydropic transfused fetuses, with an incidence of severe thrombocytopenia (<50 × 10^9 platelets/L) up to 46% [102,108,109]. This should be taken into account when performing a cordocentesis or intrauterine transfusion. Case reports of neonatal liver insufficiency [110–112] myocarditis [113–115], transfusion-dependent anemia [116,117], and central nervous system abnormalities (Cohen 1995; Yoto 1994; Adler 2010) have been reported. The general consensus is that parvovirus B19 itself, in the absence of hydrops or significant fetal anemia, does not cause long-term neurological disability, but severe anemia and fetal hydrops may be an independent risk factor for long-term neurological sequelae [104,108,118]. Therefore, fetal medicine specialists should consider cerebral imaging in fetuses or neonates who had hydrops or severe anemia. Furthermore, the myocarditis caused by parvovirus B19 can lead to severe dilated cardiomyopathy [110,113,114] and may even require heart transplantation [119].

What are the diagnostic criteria of maternal Parvovirus B19 infection?

Recommendations

- Pregnant women following contact with an infected individual, or presenting with the suggestive rash, or having a hydropic fetus should be tested for the parvovirus B19-specific IgM and IgM antibodies — *Grade: B*
- As IgM can be false negative, especially in asymptomatic patients, an IgM-negative result in a woman with a strong suspicion of parvovirus B19 infection should be complemented with molecular methods — *Grade: C*

Pregnant women presenting with a rash suggestive of Parvovirus B19 or following contact with an infected individual should be tested for the specific IgM and IgG [120,121] (Figure 5). If serology is positive (IgM and IgG), it is useful if another serum sample from before the apparent infection (e.g. from the booking blood sample in pregnancy) can be tested; if negative, this will confirm the diagnosis and help to establish the timing of the infection. If the IgM is negative and IgG is positive, these women have evidence of previous exposure and immunity and, thus, are not at risk of transplacental transmission. If the IgM is positive, regardless of IgG status, these women should be monitored for potential fetal infection. If both IgM and IgG are negative, these women

are susceptible and serologic testing should be repeated in 4 weeks. If repeat testing shows positive IgM or IgG, these pregnancies should be monitored for potential fetal infection.

High rates (20-40%) of false-negative IgM results have been reported, especially in the early asymptomatic stages when the viral load is high and the viral particles form complexes with Parvo B19-specific antibodies [122]. The clinical implications of relying on IgM solely are that some hydropic fetuses may receive a delayed IUT, or not have an IUT at all, if the IgM is false negative. Therefore, in case of strong suspicion of Parvo B19 infection with negative IgM results, the assessment should be complemented by DNA-detection methods, or the determination of IgG-avidity [122], or amniocentesis for detection of viral DNA [108].

What are the diagnostic criteria of fetal Parvovirus B19 infection?

Recommendation

- Although the viral DNA can be detected in the amniotic fluid and blood of infected fetuses, invasive testing is not indicated unless cordocentesis is being performed anyway for severe fetal anemia *GPP*

Fetal infection can be diagnosed only by invasive testing, usually by amniocentesis or occasionally by cordocentesis to obtain fetal blood. The amniotic fluid or fetal blood can be tested for the presence of parvovirus DNA by PCR. The qualitative PCR is reported to have a sensitivity as high as 100% [120]. However, as a general rule, invasive testing is not indicated unless severe fetal anemia is diagnosed by ultrasound scan [123–125], given the likelihood of coexisting thrombocytopenia [102,108,109].

How should maternal and fetal parvovirus B19 infections be managed?

Recommendations

- Serial ultrasound monitoring should start four weeks after the infection or date of seroconversion, then every 1-2 weeks after that, until 12 weeks after infection *Grade:B*

The presence of fetal hydrops is a clear indication of fetal anemia in this scenario. As mentioned above, fetal hydrops in this situation may resolve spontaneously in a third of cases. However, measuring the middle cerebral artery peak systolic velocity (MCA-PSV) is now a commonly used method of diagnosing moderate or severe fetal anemia. It has been shown that MCA-PSV > +1.50 multiples of the median (MoMs) can predict severe fetal anemia in confirmed Parvovirus B19 infection with a sensitivity and specificity of 94% and 93%, respectively [126]. Serial ultrasound monitoring should start four weeks after the infection or date of seroconversion, then every 1-2 weeks after that, until 12 weeks after infection. If severe fetal anemia is detected, cordocentesis can confirm fetal infection, as described above.

What is the recommended management of maternal and fetal Parvovirus B19 infection?

Recommendations

- Serial ultrasound, looking for evidence of ascites, cardiomegaly, hydrops fetalis or raised MCA PSV, should be performed every 1–2 weeks for 8–12 weeks after exposure. *Grade:C*
- MCA Doppler readings should not be made during or immediately after a period of fetal activity *Grade:C*
- Fetal blood sampling, with preparation for transfusion, is indicated when the MCA-PSV is greater than 1.5 MoMs, or where there is fetal ascites or hydrops. *Grade:B*
- Regarding prognosis, the parents should be informed that the risk of perinatal death is approximately 30% for fetuses presenting with hydrops vs. 6% for non-hydropic fetuses. The long-term outcome in surviving fetuses is generally good, with a 10% risk for neurodevelopmental abnormalities for hydropic fetuses *Grade:C*

Serial ultrasound, looking for evidence of ascites, cardiomegaly, hydrops fetalis or raised MCA PSV, should be performed every 1–2 weeks for 8–12 weeks after exposure. In the absence of ultrasound evidence of fetal sequelae by 8–12 weeks after exposure, adverse outcomes related to parvovirus B19 infection are highly unlikely [102,121]. Even though ultrasound monitoring focuses on fetal anemia and hydrops, fetal death can occur without evidence of hydrops fetalis [124,127].

The first large series on the performance of MCA-PSV in the prediction of moderate or severe fetal anemia reported an extremely high sensitivity and specificity, either in the setting of alloimmunization (100% and 88%, respectively) [128] or in the setting of Parvovirus infection (94% and 93%, respectively) [126]. Several publications followed, also reporting high estimates [129,130], and a 2019 meta-analysis reported sensitivity of 79% and specificity of 73% for the prediction of moderate/severe fetal anemia (any cause), when using +1.50 MoMs as cut-off for the MCA PSV [131].

MCA-PSV is easily measured while maintaining close to zero degree angle between the ultrasound beam and the direction of blood flow, thereby maintaining the accuracy of the velocity measurement. However, the MCA-PSV does not detect all cases of fetal anemia. It may not change in mild anemia; it does not increase further in cases of severe anemia when the hemoglobin concentration falls below 3g/dL; and its false positive rate increases after 35 weeks' gestation [132]

Figure 6 demonstrates the steps taken in MCA Doppler assessment, which ensure lower intra- and inter-observer variation (Mari 2005). The measurements should be obtained in the absence of fetal movement and breathing. The operators should be aware of possible pitfalls including normal variants of the MCA such as double MCA and MCA collaterals (the lenticulostriate arteries). MCA Doppler readings should not be made during a period of rest immediately following a period of fetal activity. In late gestation, the MCA Doppler measurements may also be affected by fetal heart rate accelerations or decelerations, or after uterine contractions [132,133].

Fetal blood sampling is indicated when the MCA-PSV is greater than 1.5 MoMs, or where there is fetal ascites or hydrops. When fetal anemia is confirmed by testing of fetal blood, intrauterine blood transfusion (IUT) may be indicated [118,134–136]. This reduces the risk of intrauterine fetal death (odds ratio 0.14; 95% CI 0.02 to 0.96) [137]. Fetal transfusion can return the fetal hemoglobin to a

normal level, thus helping with the resolution of cardiac failure and hydrops. Moreover, mature erythrocytes are transfused, which are less susceptible to the influence of parvovirus, and therefore likely to persist for the normal erythrocyte half-life of 120 days. A meta-analysis of observational studies showed that IUT resulted in the resolution of hydrops in 55% of affected fetuses, whereas resolution of anemia on follow-up scans was reported in all non-hydropic fetuses [138]. In most cases, this should be enough time to allow resolution of the fetal infection. Finally, transfused blood, if taken from a donor seropositive for parvovirus IgG, can confer some passive immunity on the fetus.

The common site is the placental insertion of the umbilical cord, but other options include the intrahepatic umbilical veins or the cardiac ventricles. Non-hydropic fetuses usually need only one transfusion, whereas 36% of hydropic fetuses will need two or more transfusions [138]. The risk of fetal demise depends on the presence of hydrops (29% in hydropic vs. 5.5% in non-hydropic fetuses) and the gestational age at transfusion (highest before 20 weeks) [138]. At later gestations, it may be preferable to deliver the baby early and transfuse the neonate. Fetal hydrops usually resolves within six weeks of IUT [134,135]. The ascites may persist for several weeks; this should not be regarded as failed treatment. Other congenital infections that can cause fetal anemia include cytomegalovirus, syphilis and toxoplasmosis. However, the anemia is generally not severe enough to cause fetal hydrops.

Overall, the risk of perinatal death is 30% for fetuses presenting with hydrops vs. 6% for non-hydropic fetuses. The evidence on the long-term outcomes of infected fetuses is limited, but it appears that the risk for abnormal neurodevelopment is low (approximately 10%) in hydropic and negligible in non-hydropic fetuses [118,138].

Rubella

The widespread implementation of rubella immunization has led to the elimination of rubella and congenital rubella syndrome in the WHO Region of the Americas in 2015, and 33 (62%) of 53 countries in the European Region have now eliminated endemic rubella and congenital rubella syndrome. The uptake of vaccination continues to increase internationally, and by December 2016, 152 (78%) of 194 countries were using the vaccine [139]. In the UK, routine rubella immunity testing at the pregnancy 'booking' visit has recently been discontinued because the risk of rubella infection in pregnancy is now so low; the vaccination program has led to high levels of herd immunity in the community and pregnant women (98-99% of women of childbearing age are immune) [121].

The incubation period for rubella is 14 to 21 days, and women are infectious from seven days before until seven days after the onset of the rash. In adults, including pregnant women, rubella infection is generally mild; it may be asymptomatic or consist of mild general malaise, headache, cold-like symptoms, and lymphadenopathy. This is usually followed by the rubella rash, which is diffuse, fine and maculopapular.

In contrast to most viral infections during pregnancy, the risk of fetal infection decreases with gestation; it is around 90% before 12 weeks' gestation, 55% from 12 to 16 weeks, and 45% after 16 weeks. In common with other viral infections, however, the risk of an infected fetus being affected (i.e. developing congenital defects) is greatest at earlier gestations: 97% before 12 weeks

and 20% from 12 to 16 weeks, following which there is a risk of deafness up until 20 weeks [121]. The risk of the fetus being affected as a result of primary maternal infection after 20 weeks' gestation is very small. Re-infection has been reported but the risk to the fetus in this situation is small (less than 5%) [140].

What are the diagnostic criteria of maternal rubella infection?

Recommendations

- Clinicians should be aware of the high (15-50%) false-positive rate of rubella IgM and interpret the results within the clinical context *Grade:C*

Maternal rubella infection is diagnosed by testing of serum levels of IgM and IgG. IgG is usually present within a week after the onset of the rash. IgM levels rise early but IgM assays have a 15-50% false-positive rate [141], which may be related to cross-reactivity with other viruses, long-term persistence after vaccination or even with the presence of autoantibodies [142,143]. Therefore, the diagnosis of acute rubella infection should not rely on a positive IgM test alone but should also take into account the history of relevant exposure, the development of a rash, the history of vaccination and the results of previous rubella testing [141]. Similar to other viral testing, rubella IgG avidity can help to determine the timing of infection; high avidity usually indicates infection occurring more than three months earlier [144–146], while low avidity antibodies are usually associated with infection within the previous three months.

What are the diagnostic criteria of fetal rubella infection?

Recommendations

- When primary infection occurs before 12 weeks' gestation, given the risk of fetal infection, and the risk of an infected fetus developing severe abnormalities, termination of pregnancy can be considered, even without invasive testing *GPP* *Grade:D*
- Amniocentesis performed within six weeks of the primary maternal infection carries a risk of being false-negative, therefore a negative result in these circumstances may justify repeat invasive testing later

Congenital rubella infection can have serious consequences for the fetus. Congenital rubella syndrome includes hearing loss, learning disability, heart malformations, and eye defects. As mentioned previously, the risk of fetal abnormalities is greatest when infection occurs before 16 weeks' gestation. The fetus can also be affected by growth restriction, hepatomegaly, splenomegaly, jaundice, thrombocytopenic purpura, anemia and rash. Some sequelae may present late after birth; these include late-onset deafness, eye defects, neurodevelopmental delay, and endocrinopathies.

Infection of the fetus can be confirmed by amniocentesis. This is usually delayed until after 18-20 weeks' gestation when fetal urination is established. When primary infection occurs before 12 weeks' gestation, given the risk of fetal infection and the risk of an infected fetus developing severe abnormalities, it is reasonable to offer termination of pregnancy, even without invasive

testing. As a result, invasive testing is usually performed for primary maternal infections occurring between 12 and 16 weeks of gestation (the risks to the fetus of infection after that are small).

The viral nucleic acid is detected in the amniotic fluid using PCR; this test has high sensitivity and specificity. Amniocentesis performed within six weeks of the primary maternal infection carries a risk of being false-negative [147], so a negative result in these circumstances may justify repeat invasive testing later.

Varicella-Zoster

Varicella-zoster virus (VZV), is a DNA virus of the herpes family that is highly contagious. It is transmitted by respiratory droplets and by direct personal contact with vesicle fluid or indirectly via fomites. Over 90% of pregnant women are already immune to VZV, having previously had the infection, usually in childhood. This means that primary infection in pregnancy occurs in only 3 per 1000 pregnancies [121]. Chickenpox has a characteristic rash, initially maculopapular, then becoming vesicular; the vesicles subsequently crust over, then heal completely. The rash is usually accompanied by fever and malaise. The incubation period is 10-21 days, but patients are infectious from 48 hours before the rash appears until the vesicles have finally crusted over. Maternal VZV infection during pregnancy can be serious, with significant morbidity, including varicella pneumonia, and potentially maternal death. It is also associated with the risk of perinatal mortality and morbidity.

What are the diagnostic criteria of maternal VZV infection?

Recommendations

- Non-immune pregnant women should be considered at high risk for contracting VZV if exposed to significant contact (face to face for 5 minutes or in the same room for 15 minutes or more) with an infectious patient. *Grade:D*
- For purposes of counseling, an estimate for the risk of congenital varicella syndrome is 0.5% if maternal varicella infection happened in the first 13 gestational weeks, and 2% for infections between weeks 13 and 20. The risk for congenital varicella syndrome is minimal after this point; however, there is a 25% risk of neonatal varicella if infection occurs after 36 weeks. *Grade:D*
- Pregnant women developing shingles (herpes zoster) during pregnancy should be reassured that it has not been associated with fetal or perinatal harm. *Grade:D*

The diagnosis of VZV is based on the clinical findings of a classic pruritic, vesicular rash, so laboratory testing is not usually needed. Maternal serology testing for VZV in pregnancy is usually following contact with a known case of chickenpox. The risk of infection is associated with significant contact (face to face for 5 minutes or in the same room for 15 minutes or more). If a woman gives a history of having had chickenpox previously, she can be assumed to be immune (because the rash is so characteristic), and serological testing is not essential. If she does not give such a history, testing for VZV IgG can demonstrate immunity or otherwise; a large proportion of women who do not have any known history of chickenpox infection will prove to be immune on testing. It may be possible to test the booking blood sample which is often retained in the virology laboratory until the end of pregnancy.

The risk of congenital VZV infection is the development of fetal varicella syndrome. This does not occur at the time of initial fetal infection but when there is reactivation of the virus in utero at a later stage. Although the absolute numbers are quite small, the risk of fetal varicella syndrome may be approximately 0.5% for maternal infection before 13 weeks and 2% between 13 and 20 weeks [148,149]. The risk of miscarriage does not appear to be increased if chickenpox occurs in the first trimester. If maternal infection occurs between 20 and 36 weeks of gestation, there does not appear to be any risk of fetal varicella syndrome. Infection after 36 weeks is associated with a 50% infection rate, and a 25% clinical varicella rate, in the neonate.
Maternal shingles (herpes zoster, caused by the same virus) does not carry any risk to the fetus [148].

What are the diagnostic criteria of fetal VZV infection?

Fetal varicella syndrome may include any of the following features: polyhydramnios (due to decreased movement or digestive tract atresias), limb defects and dermatomal skin scarring (due to fetal herpes zoster) and damage to the eyes and central nervous system [150–154]. Neurological defects include cortical atrophy, microcephaly, limb paresis, spinal cord atrophy, encephalitis, seizures, and Horner's syndrome. In around half of fetuses/infants, the eye will be affected by microphthalmia, chorioretinitis, cataracts or optic atrophy, and limb defects are also present in around half of the cases (Figure 7). Fetal growth restriction may be diagnosed on ultrasound scan and developmental delay may occur [150–153].

Fetal infection can be confirmed by amniocentesis; PCR can be used to detect VZV DNA. As ever, fetal infection (i.e. as confirmed by positive amniocentesis PCR) does not confirm that the fetus will be *affected* by varicella syndrome. One study [155] of nine women who suffered primary VZV infection before 24 weeks of gestation and had a subsequent amniocentesis positive for the virus, found that while four had fetuses affected, five babies were apparently unaffected. It is also worth noting that a negative amniocentesis does not completely rule out the possibility of fetal varicella syndrome developing.

What is the recommended management of maternal and fetal VZV infection?

Recommendations

• Following maternal infection in the first 20 gestational weeks, serial ultrasound scans should be commenced from five weeks after the initial maternal infection or after 16 weeks	*GPP*
• Following exposure to varicella or shingles, non-immune pregnant women should be offered VZIG within 10 days after exposure. . Oral acyclovir can also be considered as post-exposure prophylaxis.	*D*
• Oral acyclovir should be offered to pregnant women with varicella within 24 hours of developing the rash	*C*
• The option of pregnancy termination should be considered in the event of prenatal diagnosis of fetal varicella syndrome after maternal infection in the first 20 gestational weeks	*GPP*

The typical ultrasound features of varicella syndrome include microcephaly, hydrocephalus, limb defects, fetal growth restriction and soft tissue calcification [155]. In the vast majority of fetuses that develop varicella syndrome, the abnormalities can be diagnosed by five or more weeks after the initial maternal infection [156]. This suggests that serial ultrasound scans should be commenced from five weeks after the initial maternal infection or after 16 weeks of gestation.

Zoster immune globulin (ZIG) and/or acyclovir have been used in the mother in an attempt to reduce the risk or severity of fetal varicella syndrome, although there is no conclusive evidence that they are of benefit[157,158]. VZIG should be commenced up to 10 days after exposure and oral acyclovir from 7 days after exposure. Oral acyclovir appears to be safe [159]. It should also be offered if maternal lesions develop [160] and has been shown to reduce the duration of new lesion formation and the total number of new lesions and to improve constitutional symptoms, if started within 24 hours of developing the rash [161–163].

When maternal VZV infection is confirmed before 20 weeks of gestation, and fetal varicella syndrome is subsequently identified on ultrasound scan, there is a high chance of a severely affected baby and, in this situation, the offer of termination of pregnancy should be made. Where expert fetal medicine ultrasound confirms that there are no apparent fetal abnormities, the risk of neonatal sequelae is very small.

Zika virus

Transmission and prevention

Zika virus (ZIKV) is a flavivirus usually transmitted by *Aedes* mosquitoes, but it can also be transmitted from human to human through sexual contact [164–166]. A safe and effective vaccine for ZIKV is not likely to be available for several years. During the 2015-2016 epidemic, the WHO advised that pregnant women avoid travel to ZIKV affected areas, and that both men and women returning from Zika-affected areas should practise safe sex or abstinence for 6 months after their return, regardless of whether or not they had symptoms [167]. Currentely the disease is considered endemic and travelling to countries where the virus is still present is permitted with some restrictions (https://wwwnc.cdc.gov/travel/page/zika-travel-information).

Diagnosis

What are the diagnostic criteria of maternal ZIKV infection?

Recommendations

- Pregnant women should be routinely asked about their travel history. *GPP*
- Pregnant women with suggestive symptoms and a history of recent travel to an area of high or moderate ZIKV risk, or sexual contact with a person returning from an affected area, should be investigated for ZIKV *GPP*
- The primary test for ZIKV infection is real-time reverse transcription-polymerase chain reaction (rRT-PCR) of serum and urine *Grade:C*

Up to 80% of people infected with ZIKV may have minimal or no symptoms [168,169]. In the 20% that have symptoms, it is usually a mild self-limiting illness with mild fever, skin rash, conjunctivitis, muscle and joint pain, malaise, and headache. ZIKV is also associated with the development of Guillain Barré Syndrome [170]. ZIKV does not appear to affect pregnant women any differently to the general population [167,171] (Wilder-Smith 2017; WHO 2016). The incubation period for ZIKV is thought to be between 3 and 12 days [172]. Any pregnant woman presenting with these symptoms and a history of recent travel to an area of high or moderate ZIKV risk, or sexual contact with a person returning from an affected area, should be investigated for ZIKV. Pregnant women should be routinely asked about their travel history.

The primary test for ZIKV infection is real-time reverse transcription-polymerase chain reaction (rRT-PCR) of serum and urine. Antibody testing can be performed once more than a week has passed since symptom onset. Serology tests for ZIKV are prone to false-positive results due to cross-reactivity from other flaviviruses such as dengue (which is transmitted by the same vector and to which many of the ZIKV-exposed population are also exposed). For those with negative results, repeat testing may be recommended a few weeks after the last possible exposure, before ZIKV infection can be excluded with confidence [173].

What are the diagnostic criteria of fetal Zikavirus infection?

Recommendations

• A baseline fetal ultrasound should be performed after potential maternal exposure to ZIKV, with referral to an ultrasound or fetal medicine specialist in case of concerning features	*GPP*
• If the baseline scan is normal, a repeat scan in the third trimester can be considered.	*GPP* *Grade:C*
• Fetuses of mothers with a third-trimester rash and normal head circumference may still have underlying brain abnormalities and should be screened for the remaining of the pregnancy and after birth	*Grade:C*
• Pregnant women with ZIKV infection should be informed that the risk of congenital disabilities is higher with earlier infection and may be independent of the presence or absence of maternal symptoms.	

Baseline fetal ultrasound should also be performed, with referral to a fetal medicine specialist if there are any concerning features [174–176]. In women with negative ZIKV testing but fetal abnormalities such as microcephaly and intracerebral calcifications on ultrasound scan, consideration should also be given to other congenital infections including CMV, toxoplasmosis and rubella which can present with similar findings.

Exposed pregnant women with no reported symptoms during travel or within two weeks of return or possible sexual exposure should have an ultrasound for fetal growth and anatomy. If this is abnormal, referral for specialist fetal medicine review is advised. If the baseline scan is normal, a repeat scan in the third trimester can be considered. No serological testing would be advised in these cases [174].

Table 7 lists the fetal and neonatal abnormalities reported in pregnancies with Congenital Zika

Syndrome (CZS) [175,177–183].

A systematic review of 72 studies concluded that there is now sufficient evidence to confirm ZIKV as a cause of congenital brain abnormalities [170]. Congenital zika virus infection can lead to microcephaly, as well as craniofacial disproportion, specific brain abnormalities and neurological symptoms (Table 7) [177–183]. Recently, the term 'Congenital Zika Syndrome' (CZS) has been used to describe the spectrum of abnormalities associated with maternal ZIKV infection in pregnancy [175,177–184]. Infants with confirmed ZIKV infection born with a normal head circumference may still have underlying brain abnormalities [185,186]. This knowledge has important implications for counseling and neonatal screening.

The risk of CZS following infection during pregnancy, and whether this risk is related to the gestation at infection, remain unclear. One retrospective study estimated the risk of ZIKV-associated microcephaly of 95 per 10,000 women infected in the first trimester (compared with a background rate of 2 cases of microcephaly per 10,000 neonates); however, this was based on only 8 cases [187]. A prospective cohort study with a short follow up of pregnancies in the recent Brazilian outbreak found that, among live-born infants born to ZIKV-affected women, 55% had adverse outcomes if infected in the first trimester, 52% if in the second trimester and 29% if in the third trimester [177]. Preliminary analysis of data from the US Zika Pregnancy Registry has shown that among 442 completed pregnancies with laboratory evidence of possible recent ZIKV infection, 6% of the fetuses or infants had a ZIKV-associated congenital anomaly. This rate varied from 11%, for infections during the first trimester or at the periconception period, to 0% for exposure exclusively in the second or third trimester. Interestingly, the rate of congenital anomalies was very similar in symptomatic (6%; 95% CI 3-11%) and asymptomatic (6%; 95% CI 4-9%) women [188]. Comparable rates of 5% amongst symptomatic mothers and 4% amongst asymptomatic mothers were subsequently reported in a larger study from the US territories [189]. In a large cohort study that followed 301 pregnant women with laboratory proved Zika virus infections from French Guyana, fetal CNS involvement was higher in the infected than in the control group (9.0% vs 4.3%; relative risk, 2.11 (95% CI, 1.18-4.13) [190]; in a follow up paper the authors found that in cases of a known maternal Zika virus infection, approximately a quarter of fetuses will become congenitally infected, of which a third will have severe complications at birth or fetal loss [191].

Diagnosis of Congenital Zika Syndrome

Recommendations

- Microcephaly should be diagnosed when the head circumference (HC) measures ≥2 standard deviations (SD) below the mean, although a HC ≥3 SD below the mean is associated with a higher risk for brain abnormalities — *Grade:D* / *Grade:C*
- HC should not be used to ascertain gestational age in pregnancies where there has been exposure to ZIKV — *Grade:C*
- Following maternal exposure to ZIKV, an assessment of fetal anatomy (including intracerebral abnormalities) and biometry should be undertaken — *GPP*
- Any pregnancy with signs of CZS should be managed in a fetal medicine centre with experience in the diagnosis of fetal brain infections — *GPP*

- The abnormalities described in Table 7 are usually diagnosed on ultrasound; when there are doubts regarding the US findings the clinicians may consider fetal MRI where available. *Grade:4*
- Amniocentesis should not be performed for the detection of ZIKV until after 20 weeks' gestation

ZIKV infection appears to cause a characteristic pattern of brain abnormalities, which is different than these observed in cases of severe CMV infection; however, there is still much that is unknown. The mainstay of diagnosis is with fetal ultrasound examination. Microcephaly is defined as head size that is smaller than expected but it will almost never be found with normal brain imaging. Relaying only on the HC measurement with the different interpretations of this definition led to over-reporting of cases in Brazil, particularly in the early stages of the epidemic. Microcephaly should be suspected when the head circumference (HC) measures ≥2 standard deviations (SD) below the mean, although correlation with brain abnormalities is greater when the HC is ≥3 SD below the mean [167,192]. HC should not be used to ascertain gestational age in pregnancies where there has been exposure to ZIKV [176]. Microcephaly in itself is not a disease and has many different causes. However, its presence in the context of ZIKV infection should raise the suspicion of an underlying abnormality. As well as biometry measurements, an assessment of fetal anatomy, including intracerebral abnormalities, should be undertaken. Any pregnancy with signs of CZS should be managed in a fetal medicine centre with experience in fetal infections. The abnormalities described in Table 7 are usually diagnosed on ultrasound; when there are doubts regarding the US findings the clinicians may consider fetal MRI where available. Consideration should also be given to the risks and benefits of amniocentesis to test for ZIKV by rRT-PCR. The correlation of a positive amniocentesis PCR with fetal abnormality remains unclear and expert virology advice should be sought first. Amniocentesis should not be performed for the detection of ZIKV until after 20 weeks' gestation as fetal urination is not well-established before this stage and fetal urine is the source of ZIKV in the amniotic fluid [167,174,176,193]

Management of pregnancies with Congenital Zika Syndrome

Recommendations

- ZIKV-affected pregnancies should be managed in an ultrasound or fetal medicine unit with serial ultrasound scans and the availability of further laboratory testing *GPP*
- The option of termination of pregnancy should be discussed when appropriate *GPP*
- Clinicians should acknowledge the limitations of existing knowledge on the prognosis for CZS. Following a complete normal imaging follow up the risk of developing CZVS is apparently low *GPP*
- Women who continue a pregnancy with suspected congenital zika syndrome should have input from a multi-disciplinary team including fetal medicine specialists, neonatologists and radiologists, as appropriate

These pregnancies should be managed in an ultrasound or fetal medicine unit with serial ultrasound scans and the availability of further laboratory testing. Other causes of microcephaly and brain abnormalities should be considered and excluded where appropriate. Women should be counselled on an individual basis and the option of termination of pregnancy should be discussed

when appropriate. Clinicians should acknowledge the limitations of existing knowledge on the prognosis for CZS but following a complete normal imaging follow up the risk of developing CZVS are apparently low [191]. In other congenital viral infections, such as CMV and toxoplasmosis, which can cause similar brain abnormalities, the presence of microcephaly would suggest a poor prognosis whilst normal ultrasound findings would suggest a good prognosis [34,89,167]. However, this may not be entirely true of ZIKV where, as described above, brain abnormalities have been found in infants with a normal HC [185,186]. Women who continue pregnancy with suspected CZS should have input from a multi-disciplinary team including fetal medicine specialists, neonatologists and radiologists, as appropriate. After birth, follow-up until at least 12 months of age is recommended [194].

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172

174 **Table 1**. Ultrasound signs suggestive of congenital infection

Cranial abnormalities	**Extra-cranial abnormalities**	**Placental/Amniotic fluid abnormalities**
Ventriculomegaly	Small for gestational age	Placentomegaly
Calcifications	Hyperechogenic bowel	Placental calcifications
Intraventricular synechiae	Hepatomegaly-splenomegaly	Oligohydramnios/anhydramnios
Cerebellar abnormalities: vermian hypoplasia, cerebellar hemorrhage, calcifications, cysts	Liver calcifications	Polyhydramnios
Periventricular pseudocysts	Ascites	
Malformations of cortical development: lissencephaly-pachygyria, oligo-/pachygyria, polymicrogyria, schizencephaly	Pericardial effusion	
Microcephaly	Skin edema	
	Hydrops or fetal anaemia (middle cerebral artery peak systolic velocity above 1.5 multiples of median) in the absence of maternal atypical antibodies	

175

177 **Table 2.** The frequency of abnormal ultrasound findings in pregnancies complicated by
178 congenital cytomegalovirus infection (Guerra 2008)

Ultrasound finding	**Frequency (%)**
Ventriculomegaly	4.5-11.6
Calcifications	0.6-17.4
Microcephaly	14.5
Subependymal cysts	11.6
Intrauterine growth retardation	1.9-13
Hyperechogenic bowel	4.5-13
Hepatomegaly	4.3
Liver calcifications	1.4
Placentomegaly, calcifications	4.3
Ascites	8.7
Pericardial effusion	7.2
Hydrops	0.6
Hyperechogenic kidneys	4.3

Table 3. Criteria to define a moderately-infected fetus, according to the inclusion criteria in the study by Leruez-Ville et al (Leruez-Ville 2016).

Leruez-Ville M, Ghout I, Bussieres L, Stirnemann J, Magny JF, Couderc S, et al. In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study. Am J Obstet Gynecol 2016;215:462.e1-462.e10.

At least 1 extracerebral abnormality compatible with fetal CMV infection	
	Fetal growth restriction
	Abnormal amniotic fluid volume
	Ascites and/or pleural effusion
	Skin oedema
	Hydrops
	Placentomegaly >40mm
	Hyperechogenic bowel
	Hepatomegaly >40mm
	Splenomegaly >30mm
	Liver calcifications
And/or 1 isolated cerebral abnormality	
	Moderate isolated ventriculomegaly (<15mm)
	Isolated cerebral calcification
	Isolated intraventricular adhesion
	Vasculopathy of lenticulostriate vessels
And/or laboratory findings of generalised CMV infection in fetal blood	
	Fetal viraemia >3000 copies/mL
	Fetal platelet count <100,000/mm^3

188 **Table 4.** Risk of Toxoplasma gondii congenital infection (transmission) and development of clinical signs in offspring before age 3 years,
189 according to gestational age at maternal seroconversion (Dunn 1999).

Gestational age at maternal seroconversion, weeks	Risk of congenital infection (95% CI), %	Development of clinical signs in the infected offspring (95% CI), %	Risk of development of clinical signs when infection status is unknown, %
13	6 (3-9)	61 (34-85)	4
26	40 (33-47)	25 (18-33)	10
36	72 (60-81)	9 (4-17)	7

190 Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical
191 counselling. Lancet 1999; 353:1829–33.
192 Montoya JG, Remington JS. Management of Toxoplasma gondii infection during pregnancy. Clin Infect Dis 2008;47:554-66.
193

Table 5. Interpretation of results of serological tests for toxoplasmosis performed at clinical (non-reference) laboratories.

IgG test result	IgM test result	Clinical relevance
Negative	Negative	No evidence of maternal infection during pregnancy.
Positive	Negative	During the first or second trimester, likely indicated pre-pregnancy infection. If in the third trimester, this result is more difficult to interpret. Although it is most consistent with an infection acquired pre-pregnancy, in some patients, this result may reflect an infection that was acquired early in gestation and that was accompanied by an increase in the IgM titer and a decrease to non-detectable levels within a relatively brief period of time.
Negative	Positive or equivocal	Positive (or equivocal) IgM test result should be followed by confirmatory testing at a Toxoplasma reference laboratory. IgM antibodies are detected early in the acute infection and may persist for years.
Positive	Positive or equivocal	Positive (or equivocal) IgM test result should be followed by confirmatory testing at a Toxoplasma reference laboratory. IgM antibodies are detected early in the acute infection and may persist for years.

Montoya JG, Remington JS. Management of Toxoplasma gondii infection during pregnancy. Clin Infect Dis 2008;47:554-66.

Table 6. Ultrasound abnormalities in fetuses infected by Parvovirus B19 (from Benoist G and Ville Y. Fetal infections. In: Rodeck CH, Whittle MJ, eds. Fetal Medicine: Basic science and clinical practice. London: Churchill Livingstone, 2009.)

Cardiac system	• Increased cardiac biventricular outer diameter • Myocarditis
Non-immune hydrops fetalis	• Pleural effusion • Pericardial effusion • Ascites • Abdominal wall oedema • Bilateral hydroceles • Amniotic fluid disorder
Brain abnormalities*	• Hydrocephalus • Microcephaly • Intracranial calcification
Gastrointestinal system	• Fetal liver calcification • Meconium peritonitis
Other findings	• Sporadic cases of contractures • Increased nuchal translucency • Intrauterine growth restriction

*Following brain haemorrhage

Table 7. A list of the fetal and neonatal abnormalities reported in pregnancies with Congenital Zika Syndrome (CZS) (Brasil 2016; Chibueze 2017; Brasil 2016; Hazin 2016; Soares 2016; de Fatima 2016; de Paula 2016; Ventura 2016). Adapted from Public Health England. Zika virus congenital infection: interim guidance for neonatologists and paediatricians (Public Health England 2016).

Public Health England: Zika virus congenital infection: interim guidance for neonatologists and paediatricians.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/543979/Zika_neonatal_guidance.pdf (2016). Accessed 16 August 2017.

Neuro-imaging Findings	**Clinical Findings**
Cerebral and cerebellar atrophy	Microcephaly
Cerebral calcifications	Craniofacial disproportion
Cortical and white matter abnormalities (e.g. agyria, pachygyria, lissencephaly)	Redundant scalp skin
Ventriculomegaly	Closed anterior fontanelle
Internal hydrocephalus	Exuberant external occipital protuberance
Periventricular cysts	Intrauterine growth restriction
Choroid plexus cyst	Contractures
Blake's cyst	Talipes
Mega cisterna magna	Umbilical hernia
Vermian dys-/agenesis	Hypertonia or spasticity
Callosal abnormalities	Hyperreflexia
Brain stem/spinal cord degeneration	Irritability
Ocular abnormalities (intraocular calcifications, cataracts, microphthalmia, macular alterations, optic nerve abnormalities	Convulsions, tremors
	Hearing and visual abnormalities

Brasil P, Pereira JP Jr, Raja Gabaglia C, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro - Preliminary Report. *N Engl J Med* 2016. doi:10.1056/NEJMoa1602412

Chibueze EC, Tirado V, da Silva Lopes K, et al. Zika virus infection in pregnancy: a systematic review of disease course and complications. *Reproductive Health* 2017;14:28 DOI: 10.1186/s12978-017-0285-6

Brasil P, Pereira Jr JP, Moreira ME, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro. N Engl J Med 2016; 375:2321-2334.

Hazin AN, Poretti A, TurchiMartelli CM, et al. Computed tomographic findings in microcephaly associated with Zika virus. *N Engl J Med* 2016;374:2193–5.

Soares de Oliveira-SzejnfeldP, Levine D, Suely de Oliveira Melo A, et al. Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally. *Radiology*. 2016;281:2.

de Fatima Vasco Aragao M, van der Linden V, Brainer-Lima AM, et al. Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. *BMJ* 2016;353:i1901.

de Paula FrietasB, de Oliviera Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brasil. *JAMA Ophthalmol* 2016. Doi: 10.1001/jamaophthalmol.2016.0267.
Ventura CV, Maia M, Ventura BV, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. *Arq Bras Oftalmol* 2016;79:1-3.

Classification of evidence levels

1++ High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a low risk of bias

1- Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g. case reports, case series

4 Expert opinion

Grades of recommendations

A At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or a systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

GPP Recommended best practice based on the clinical experience of the guideline development group

FIGURE LEGENDS

Figure 1. Ultrasound findings in fetuses with congenital CMV infection. They can be categorized as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormality. The ultrasonographic cranial features of CMV infection vary but include ventriculomegaly, microcephaly, calcifications, increased periventricular echogenicity or halo, periventricular pseudocysts, intraventricular synechiae, abnormalities of cortical development and of the cerebellum and posterior fossa, or cerebral hemorrhage. Extracranial fetal abnormalities also vary but include splenomegaly, hepatomegaly, hyperechogenic bowel, isolated pleural or pericardial effusion, ascites, fetal hydrops and cardiomegaly.

Figure 2. Proposed management of congenital CMV infection (adopted from Benoist et al 2013)

Figure 3. Ultrasound findings in fetuses with congenital toxoplasma infection.

Figure 4. Ultrasound findings in fetuses with congenital parvovirus B19

Figure 5. Investigation for parvovirus B19 of pregnant women exposed to rash illness. (Adapted from the 2000 Public Health Laboratory Service Working Party on 'Rash Diagnosis in Pregnancy and Rubella Screening', subsequently reported)

Figure 6. Technique of measuring the middle cerebral artery Doppler

Figure 7. Ultrasound findings in fetuses with congenital rubella

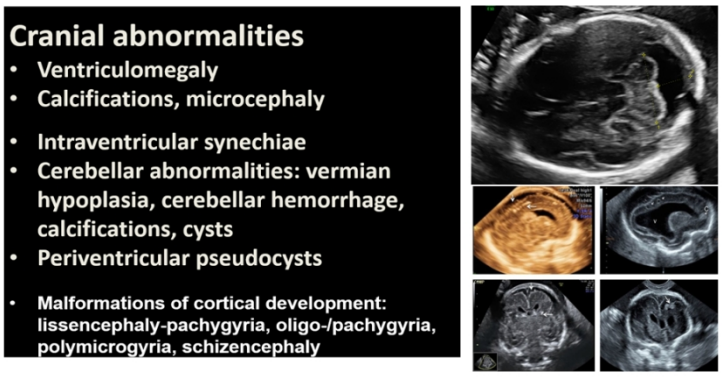

Figure 1a

Figure 1a. Ultrasound findings in fetuses with congenital CMV infection. They can be categorized as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormality. The ultrasonographic cranial features of CMV infection vary but include ventriculomegaly, microcephaly, calcifications, increased periventricular echogenicity or halo, periventricular pseudocysts, intraventricular synechiae, abnormalities of cortical development and of the cerebellum and posterior fossa, or cerebral hemorrhage. Extracranial fetal abnormalities also vary but include splenomegaly, hepatomegaly, hyperechogenic bowel, isolated pleural or pericardial effusion, ascites, fetal hydrops and cardiomegaly.

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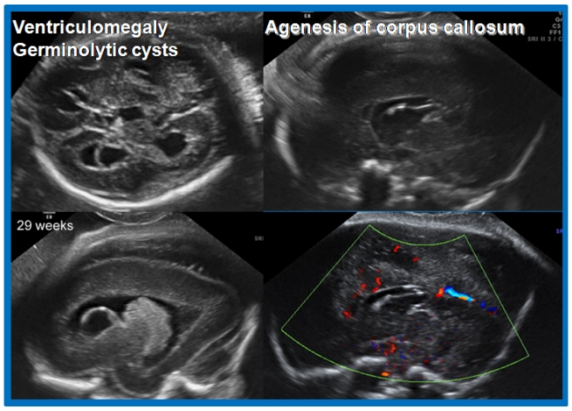

Figure 1b

Figure 1b. Ultrasound findings in fetuses with congenital CMV infection. They can be categorized as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormality. The ultrasonographic cranial features of CMV infection vary but include ventriculomegaly, microcephaly, calcifications, increased periventricular echogenicity or halo, periventricular pseudocysts, intraventricular synechiae, abnormalities of cortical development and of the cerebellum and posterior fossa, or cerebral hemorrhage. Extracranial fetal abnormalities also vary but include splenomegaly, hepatomegaly, hyperechogenic bowel, isolated pleural or pericardial effusion, ascites, fetal hydrops and cardiomegaly.

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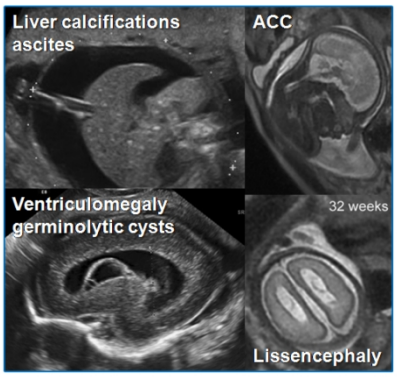

Figure 1c

Figure 1c. Ultrasound findings in fetuses with congenital CMV infection. They can be categorized as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormality. The ultrasonographic cranial features of CMV infection vary but include ventriculomegaly, microcephaly, calcifications, increased periventricular echogenicity or halo, periventricular pseudocysts, intraventricular synechiae, abnormalities of cortical development and of the cerebellum and posterior fossa, or cerebral hemorrhage. Extracranial fetal abnormalities also vary but include splenomegaly, hepatomegaly, hyperechogenic bowel, isolated pleural or pericardial effusion, ascites, fetal hydrops and cardiomegaly.

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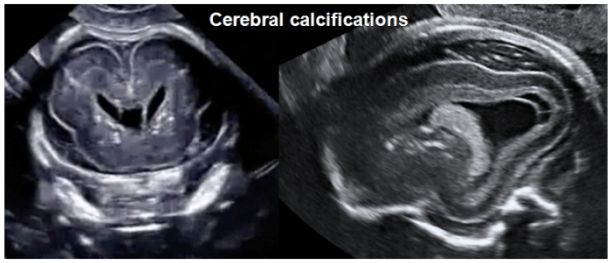

Figure 1d

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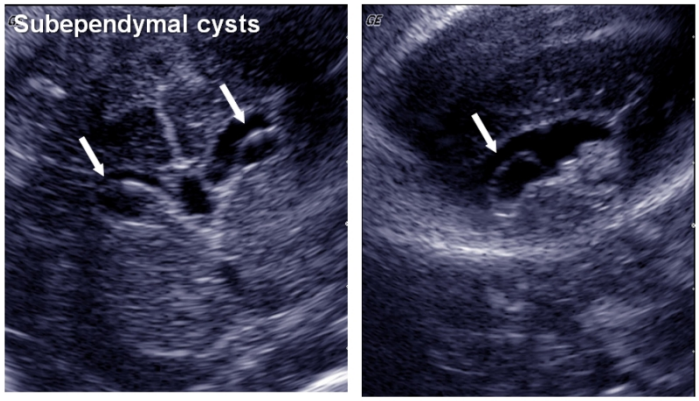

Figure 1e

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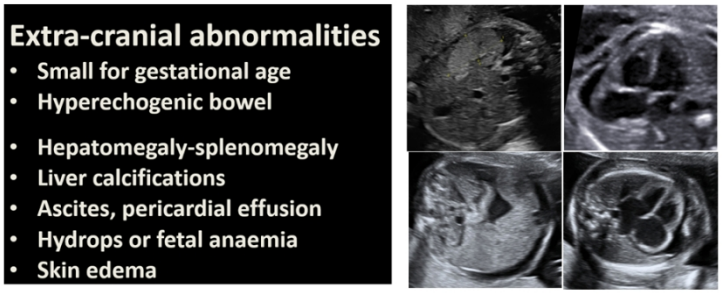

Figure 1f

Figure 1f. Ultrasound findings in fetuses with congenital CMV infection. They can be categorized as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormality. The ultrasonographic cranial features of CMV infection vary but include ventriculomegaly, microcephaly, calcifications, increased periventricular echogenicity or halo, periventricular pseudocysts, intraventricular synechiae, abnormalities of cortical development and of the cerebellum and posterior fossa, or cerebral hemorrhage. Extracranial fetal abnormalities also vary but include splenomegaly, hepatomegaly, hyperechogenic bowel, isolated pleural or pericardial effusion, ascites, fetal hydrops and cardiomegaly.

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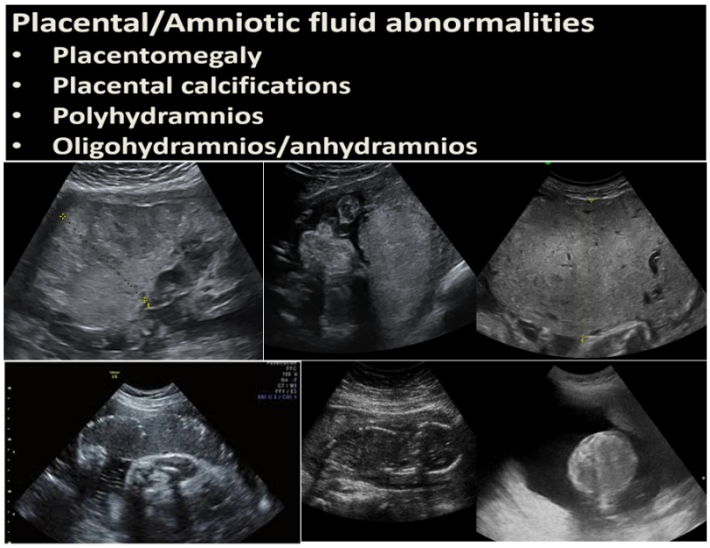

Figure 1g

Figure 1g. Ultrasound findings in fetuses with congenital CMV infection. They can be categorized as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormality. The ultrasonographic cranial features of CMV infection vary but include ventriculomegaly, microcephaly, calcifications, increased periventricular echogenicity or halo, periventricular pseudocysts, intraventricular synechiae, abnormalities of cortical development and of the cerebellum and posterior fossa, or cerebral hemorrhage. Extracranial fetal abnormalities also vary but include splenomegaly, hepatomegaly, hyperechogenic bowel, isolated pleural or pericardial effusion, ascites, fetal hydrops and cardiomegaly.

338x190mm (96 x 96 DPI)

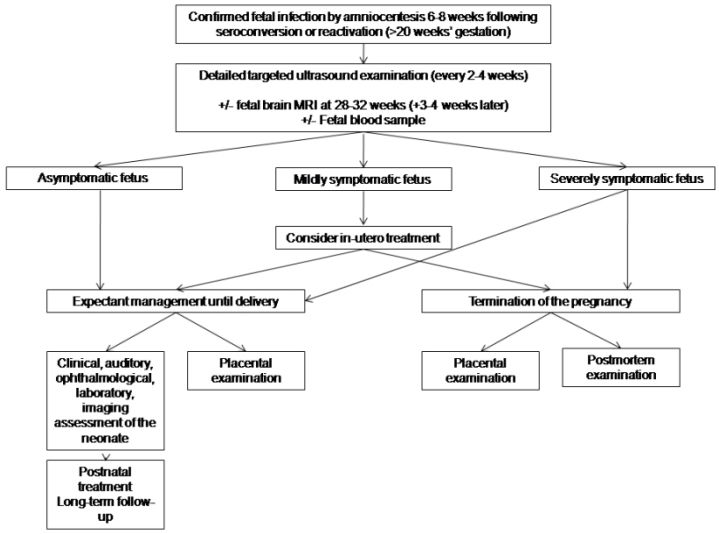

Figure 2.

Figure 2. Proposed management of congenital CMV infection (adopted from Benoist et al 2013)

338x190mm (96 x 96 DPI)

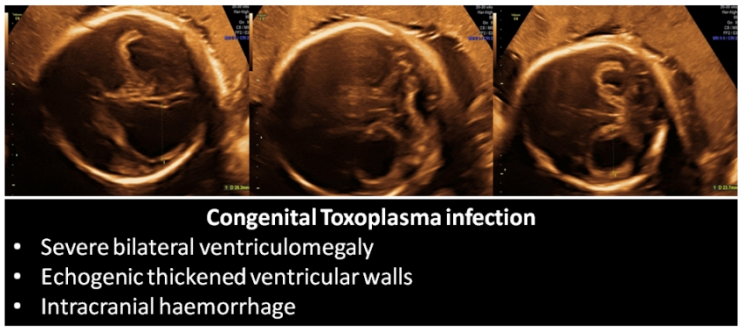

Figure 3

Figure 3. Ultrasound findings in fetuses with congenital toxoplasma infection

338x190mm (96 x 96 DPI)

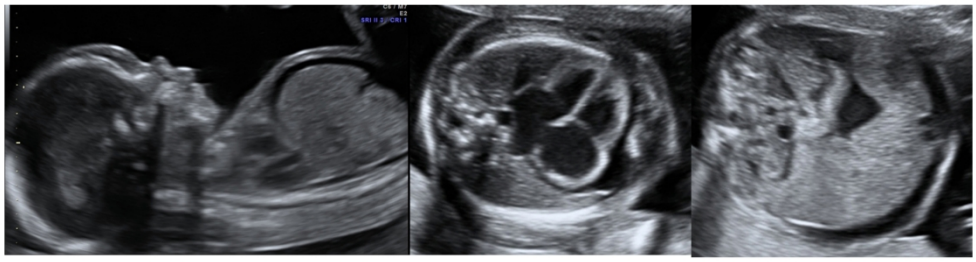

Figure 4

Figure 4. Ultrasound findings in fetuses with congenital parvovirus B19

338x190mm (96 x 96 DPI)

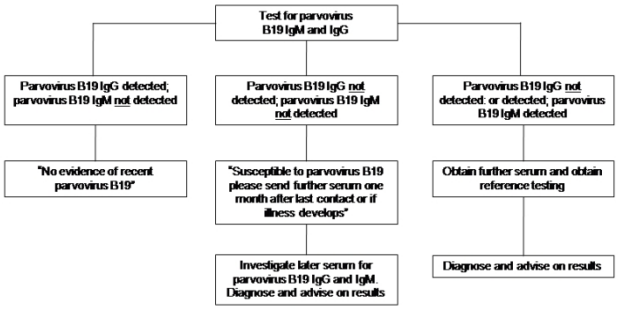

Figure 5

Figure 5. Investigation for parvovirus B19 of pregnant women exposed to rash illness. (Adapted from the 2000 Public Health Laboratory Service Working Party on 'Rash Diagnosis in Pregnancy and Rubella Screening', subsequently reported)

338x190mm (96 x 96 DPI)

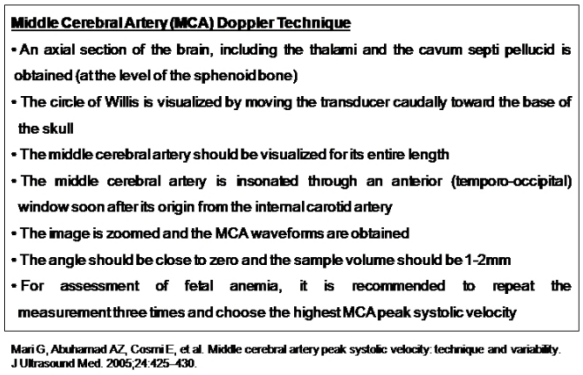

Figure 6a. Technique of measuring the middle cerebral artery Doppler

338x190mm (96 x 96 DPI)

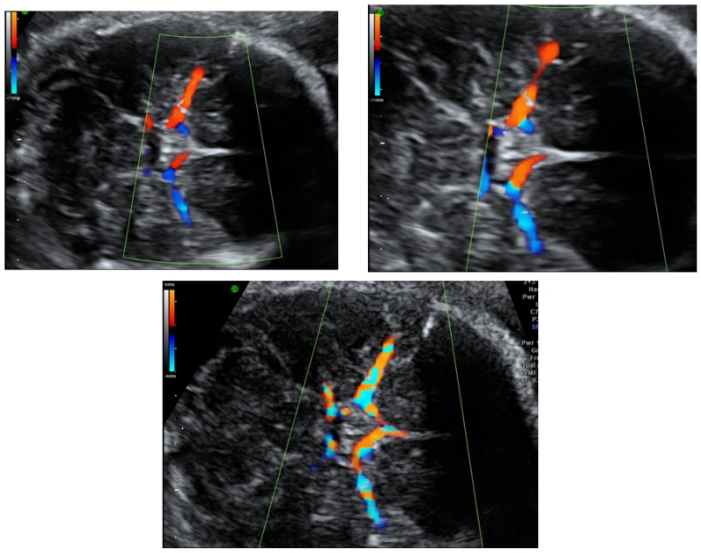

Figure 6b

Figure 6b. Technique of measuring the middle cerebral artery Doppler

338x190mm (96 x 96 DPI)

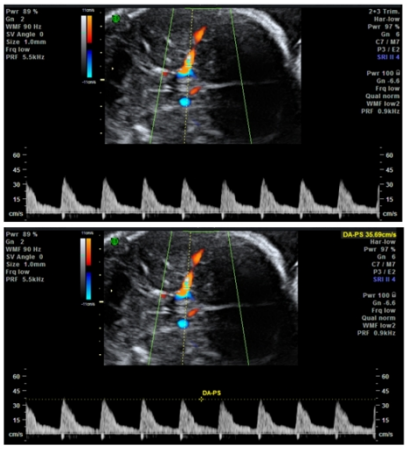

Figure 6c

Figure 6c. Technique of measuring the middle cerebral artery Doppler

338x190mm (96 x 96 DPI)

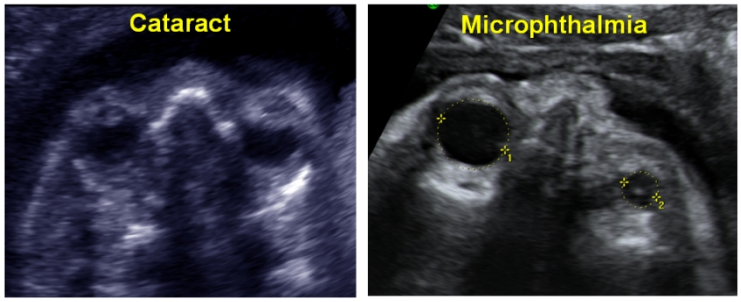

Figure 7

Figure 7. Ultrasound findings in fetuses with congenital rubella

338x190mm (96 x 96 DPI)