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Ultrasound diagnosis of infections in pregnancy

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ABSTRACT

Pregnancy is a unique period in which several changes occur in the mother, to ensure that the semiallograft fetus is not rejected. Some of these changes decrease the immunity of the mother to infections. As such, some infections in pregnancy which may not ordinarily cause severe symptoms can be more severe in the mother and importantly some of these infections pose a danger to the fetus either directly or indirectly. In dealing with infections in pregnancy, attention should focus on both the consequences of the infection on the mother as well as in the fetus. Over the last decade, some of these infections have significantly influenced clinical practice. This series on Infections in Pregnancy in this journal provides a comprehensive cover of this topic. Here we focus on the fetal impact of infections in pregnancy and how ultrasound scan can help in identifying some of these infections and more importantly map out pathways for managing the pregnancies including counselling and additional invasive procedures.

Introduction

Infections in pregnancy may either be symptomatic or asymptomatic, making it difficult to estimate just how common these are. Most have no effects but some have varying consequences on both the mother and the fetus, influenced no doubt by the impact of pregnancy on the immune status of the woman [1]. Infections that may affect the fetus can be viral, bacterial, protozoal or fungal.

Amongst the viral infections are rubella, cytomegalovirus, herpes simplex, hepatitis, varicella zoster, zika, parvovirus B19, human immunodeficiency virus, Coronavirus and *Coxsackie virus*. Bacterial infections include *Treponema pallidum*, *Listeria monocytogenes*, *Chlamydia trachomatis*, *Neisseria gonorrhoea, Mycobacterium tubercluli* and *Bordetella pertussis* while protozoan infections include *Toxoplasma gondii* and fungi include *Candida albicans*.

When pregnant women present with specific symptoms/signs of infections, appropriate serological investigations are often instituted to help make a diagnosis. However, with regards to fetal infections, ultrasound is an essential tool in identifying definite cases of intrauterine infections and those with suspected intrauterine infections requiring further investigations.

Frequently, it is the initial abnormal ultrasound findings that triggers maternal serological testing for congenital infections. In some cases, the diagnosis of infections from routine screening tests performed in pregnancy or based on the mother's symptomatology triggers targeted ultrasound scans with the aim of detecting fetal sequelae.

Once a congenital infection is diagnosed, ultrasound can be used to help gauge fetal prognosis and guide further investigations and management. In this review which complements the articles on various infections in pregnancy in this special issue, we highlight the typical ultrasound features associated with specific infections and the role of ultrasound in diagnosis and management especially of complications of congenital infections such as fetal anaemia.

Viral infections

Cytomegalovirus (CMV)

CMV is the most common viral infection in pregnancy as well as the most common viral cause of congenital infections. Congenital CMV affects 0.2–2.5 % of all live births, is the leading non-genetic cause of sensorineural hearing loss and a major cause of

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neurological disability. Around 5–10 % of neonates with congenital CMV will be symptomatic at birth, and up to 25 % of infected neonates have long-term impairments [2–6].

When a susceptible woman has the infection for the first time, she is said to have a primary infection and when it is a subsequent infection, these are referred to as secondary. The consequences of the infection both to the mother and the fetus depend on whether it is a primary or secondary/subsequent (reinfection) infection. For example, with a primary infection, the risk of fetal involvement is up to 40 % but with secondary infection (reinfection) this is less than 2 % [7]. This difference is as a result of the impact of the infection on the maternal immunity - a prior infection modifies maternal immunity reducing not only the consequences on the mother but the risk of vertical transmission. Most CMV infections are asymptomatic (>90 % for primary and 85 % for secondary) and the others (<10 %) present with non-specific symptoms such as flu-like symptoms, myalgia, fever and body aches [2,8]. The risk of vertical transmission is, however, independent of whether the patient is symptomatic or not [8].

The rate of vertical transmission after primary maternal infection is on average about 30–40 %; it increases with gestational age from an average of 35 % in the first trimester, to 42 % in the second trimester and to 47–78 % in the third trimester [8,9]. While the risk of vertical transmission is greatest in the third trimester, the consequences are greatest for transmission in the first trimester. Intrauterine infection induces changes in the placenta which vary from none (normal placenta) to widespread villous destruction by extensive inflammation. This inflammation may vary from diffuse villitis, plasma infiltration to focal necrosis and haemorrhage without detectable cells with typical inclusions in the placenta [10].

Intrauterine infection with CMV causes a wide spectrum of pathologies in the fetus and placenta. Antenatally, a high index of suspicion based on the classical features of congenital CMV infection is crucial in making a diagnosis. These features include;

(1) Placental – calcification (either widespread of circumscribed), pale and oedematous – presenting as placentomegaly
(2) Central nervous system – intraventricular adhesions, periventricular halo, microcephaly, periventricular calcifications and necrosis, hydrocephalus, chorioretinitis, cataract and microphthalmia
(3) Chest – Pericardial effusion, cardiomegaly, calcifications in the heart (atrium and ventricles) and pleural effusion
(4) Abdomen – hepatosplenomegaly, hepatic echogenicity (widespread calcifications in the liver), ascites; rarely peripheral echogenic rings (around the kidneys) and disorganised renal parenchyma
(5) Skeletal - these are less obvious and tend to be present on X-ray. CMV causes periosteal inflammation and sclerotic bone lesions alternating with demineralized areas producing the classical radiological fetuses of “celery-stalk lesion) or longitudinal streaking of metaphyses of long bones (also found in congenital rubella)
(6) Others – polyhydramnios and fetal hydrops

Confirmation of fetal infection is usually from amniotic fluid viral PCR (best obtained > 6 weeks after maternal infection and after 20 weeks of gestation). For those severely affected e.g. with microcephaly, termination of pregnancy may be an option depending on statutes of the country. Ultrasound is therefore useful in providing guidance on relative prognosis in severe cases (like diagnosing severe brain abnormalities) which can be confirmed by fetal MRI. Serial ultrasound scan is recommended to monitor growth and intracranial development following a diagnosis. At the time of birth, most infected babies are

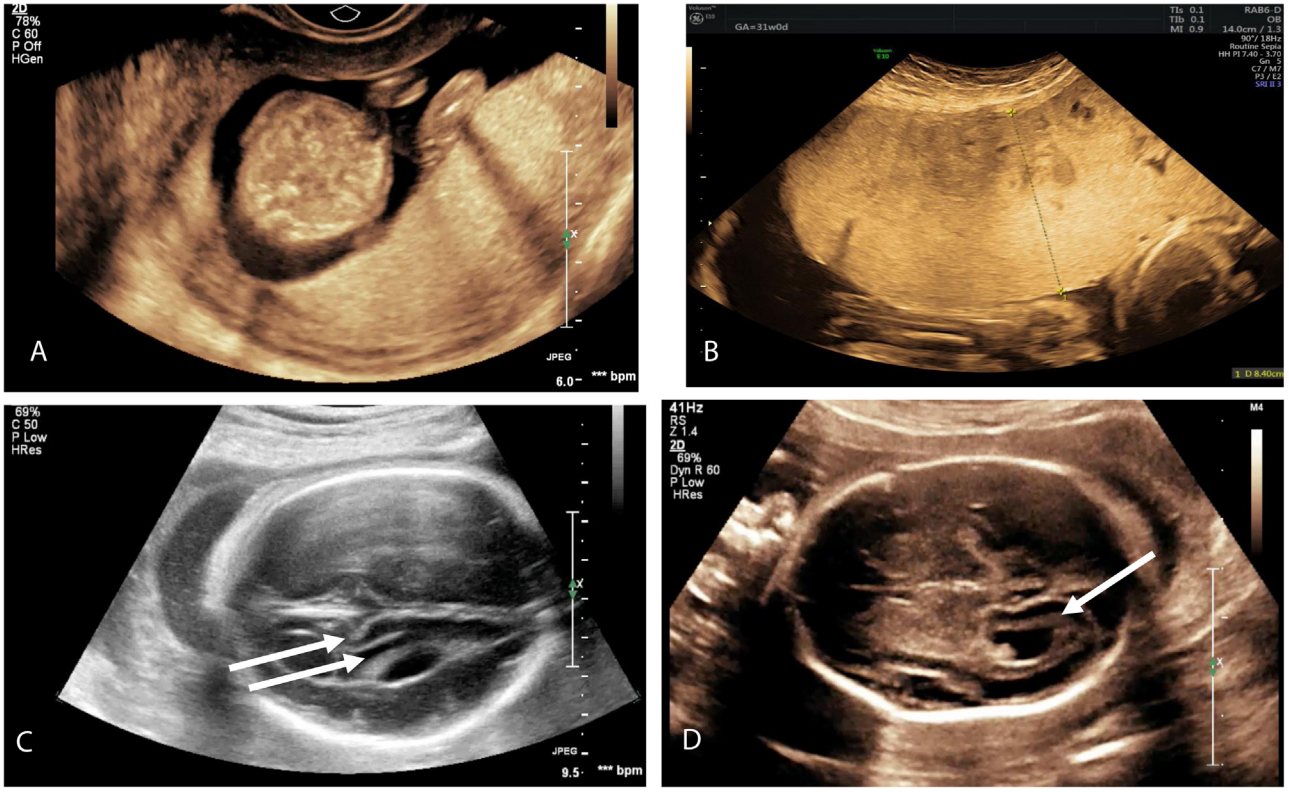

Fig. 1. 4 images from fetuses infected with CMV. Figure 1AHyperechogenic bowel in a fetus with congenital CMV Infection, 1B shows placentomagaly, 1C shows periventricular adhesions (arrow) in a fetus with congenital CMV infection and 1D shows abnormal periventricular hyperechogenicity (Halo sign) (arrow)in a fetus with congenital CMV Infection.

asymptomatic, but up to 5–10 % may present with a combination of features including growth restriction, hepatosplenomegaly, thrombocytopenia, jaundice, haemolytic anaemia, purpura, viral pneumonia, viral encephalitis, chorioretinitis, hypotonia, cerebral calcifications, jaundice (hyperbilirubinaemia) and thrombocytopenic purpura [11–13]. Fig. 1 shows some of the typical features of congenital CMV.

Rubella

The Australian clinician Sir Gregg was the first to associate Rubella with congenital malformations [14]. The incubation period for rubella is 14–21 days, and individuals are infectious from 7 days before and until 10 days after onset of the rash. In adults, including pregnant women, rubella infection is generally mild; it may be asymptomatic or present with mild malaise, headaches, cold-like symptoms and lymphadenopathy. This is usually followed by the rubella rash, which is diffuse, fine and maculopapular.

Rubella immunisation has thankfully reduced to very low levels susceptibility to Rubella virus (with the WHO for example declaring the Americas as a rubella free zone). The virus passes through the placenta to the fetus throughout pregnancy with the vertical transmission rate highest in the third trimester. However, the risk of fetal infections and consequences are greatest with vertical transmission in the first trimester [15,16]. The sequelae of intrauterine Rubella infection depend on the gestational age of the infection. The risk of congenital malformations (which tend to be major) decreases with increasing gestational age at maternal infection; it is around 85–95 % before 12 weeks' gestation, 20 % from 12 to 16 weeks while infection from 16 to 20 weeks is associated with a minimal risk of deafness only [15,16]. The risk of the fetus being affected as a result of primary maternal infection after 20 weeks' gestation is very small. Nearly all fetal infections occur following primary maternal infections although there have been reported cases following maternal reinfection with a reported risk of <5 % [17,18]. Some of the sequelae of intrauterine rubella infection may, however, appear as late as at 8 years of life [16]. Table 1 shows the rate of malformations and congenital infections at different gestational ages.

Following intrauterine infection, the virus invades the placenta and causes damage to the villous vessels followed by villous oedema. There is an increase in Hofbauer cells (placental villous macrophages) and in some cases there will be placental haemorrhage and necrosis [19]. These changes have a negative impact on the changes to placentation - the normal trophoblastic invasion that is associated with normal pregnancy does not occur hence there is an increase in uterine artery resistance as evidenced by an abnormal uterine Doppler (raised pulsatility index (PI) or resistance index (RI) and the presence of notching). With infections close to term, the changes on the villi do not affect the uterine artery Dopplers but there may be a sudden reduction in uteroplacental perfusion followed by intrauterine hypoxia and fetal death [20]. The placenta in this case will appear small, fibrotic or calcified.

The classical triad of congenital rubella include cataracts, sensorineural deafness and congenital heart diseases [2]. Sensorineural deafness, however, is a manifestation diagnosed after delivery. The typical ultrasound features in fetuses with congenital rubella include:

1 Cranial – micrognathia, microcephaly, dystrophic calcifications, cataracts, microphthalmia
2 Chest – cardiac malformations
3 Abdomen – hepatosplenomegaly
4 Calcifications – placenta, liver, myocardium, kidney, spinal cord, eyes and musculoskeletal
5 Hydrops
6 Placentomegaly
7 Fetal growth restriction

Neonatal abnormalities include hepatomegaly, jaundice, thrombocytopenic purpura, anaemia and a rash. Some sequelae may present later after birth; these include late-onset deafness, eye defects, neurodevelopmental delay, and endocrinopathies. Intrauterine infection can be confirmed by amniocentesis and viral PCR. 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 consider termination of pregnancy when appropriate, even without invasive testing as mentioned earlier [2].

Fig. 2 shows some of the malformations on USS in congenital rubella infection

Human parvovirus B-19

Parvovirus B-19 is a viral infection common in 2–12 year-old children. It causes erythema infectiosum or slapped cheek disease and is also known as the 5th disease [2]. The estimated annual incidence is 1:400 pregnancies. Susceptibility to this infection varies but approximately 40 % of individuals who are older than 12 years are susceptible. 50 % of pregnant women who are seronegative are at risk of Parvovirus B-19 infection [21–24]. Pregnant women most at risk are those who work closely with school children.

Vertical transmission occurs throughout pregnancy, however the effects on the fetus in late pregnancy are less marked. Transplacental transfer occurs in about 30 % of infected pregnant women and the risk of intrauterine fetal death in these cases is

Table 1
Rates of vertical transmission with gestational age and risks of major malformations.

Gestational age	Risk of vertical transmission	Risk of malformation
<12 weeks	90 %	97 %
12–16 weeks	55 %	20 %
16–20- weeks	45 %	Minimal

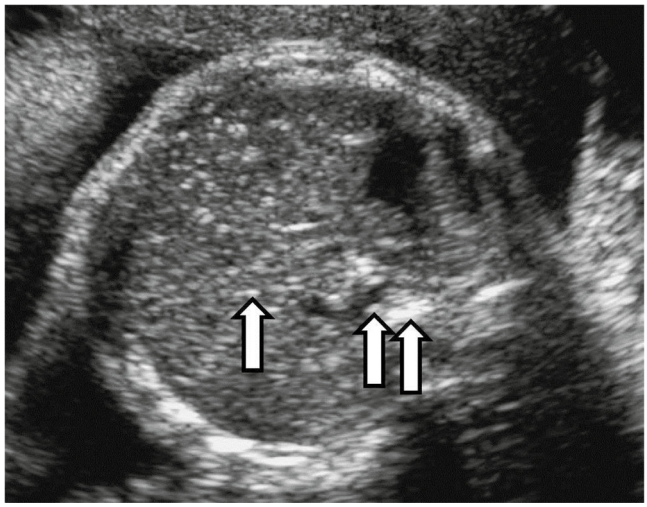

Fig. 2. Abdomen of a fetus with congenital Rubella infection showing scattered echogenicities (arrows) within an enlarged liver *From Bailao et al. Ultrasound Quarterly, 2005;21:4.*

<10 %; the greatest risk for adverse fetal outcome is between 3–6 weeks following maternal infection [21–24]. The virus on getting to the fetus enters erythroid progenitor cells where it replicates and inhibits maturation. As a result, the fetus develops anaemia, congestive cardiac failure, hydrops and fetal death in most cases, especially if untreated. It is estimated that approximately 3 % of fetal infections with parvovirus B19 result in non-immune hydrops. The virus is also able to infect heart muscles causing a myocarditis, which may also lead to heart failure.

Congenital infection with Parvovirus B-19 is the most common cause of treatable non-immune hydrops. The hydrops secondary to Parvovirus-B19 is associated with a hyperdynamic circulation – there is pulmonary congestion (pleural effusion), cardiomegaly, hepatomegaly and ascites. Hydrops develops clinically when the deficit in fetal Hb is more than 7 g/dl [2]. Since severe fetal anaemia does not occur before 16 weeks of gestation with Rhesus isoimmunisation, the presence of features of fetal anaemia prior to this time (for example cardiomegaly with increased nuchal translucency) should give rise to a high suspicion of infection with parvovirus-B19. For chromosomally normal fetuses, the prevalence of Rubella, CMV and herpes *where there is an abnormal NT* is not greater than in the general population hence there is no need to investigate for these infections unless the NT progresses to nuchal oedema or fetal hydrops. However, because Parvovirus-B19 infects the heart and causes myocardial dysfunction or anaemia from suppression of haematopoiesis, it may result in an abnormal NT as an early manifestation requiring investigation [25]. Congenital malformations are not associated with parvovirus-B19 infection.

The ultrasound features of intrauterine parvovirus B-19 infection include hepatosplenic calcifications, hydrops (pleural effusion, ascites, cardiomegaly, skin oedema and hepatosplenomegaly), mild hydrocephaly, placental oedema with or without hydropic degeneration and polyhydramnios. The management is by serial monitoring with peak systolic velocity (PSV) of Dopplers of the middle cerebral artery and when hydrops occurs or there is anaemia offering intrauterine transfusion [26]. Serial monitoring should be continued for 10 weeks following maternal infection.

Invasive testing is not routinely indicated unless there is severe fetal anaemia suspected on the basis of a middle cerebral artery Doppler peak systolic velocity of >1.5MoM (Fig. 3D), or when there is fetal ascites or hydrops diagnosed by ultrasound. At this procedure anaemia is confirmed by testing fetal blood and intrauterine blood transfusion instituted to reduce the risk of intrauterine fetal death. The risk of fetal demise associated with parvovirus-B19 depends on two main factors – hydrops (it is 30 % if the fetus is hydropic and 6–10 % if it is not) and the gestational age at transfusion (the highest risk is for hydrops developing before 20 weeks). At later gestations, it may be preferable to deliver the baby early and transfuse the neonate. Fetal hydrops usually resolves within 6 weeks of intrauterine blood transfusion [2]. Fig. 3 show some features of fetal hydrops in Parvovirus B-19 infection.

Herpes simplex virus (HSV)

HSV infections occur in the nasolabial and genital areas. There are two types – Type 1 and Type 2. Both infect the genital tract but Type 2 is predominantly genital while Type 1 is predominantly oral. Spread is by direct contact with infected secretions. The prevalence of HSV varies depending on the socio-economic status of the population. Some studies have reported seropositive antibody prevalence rates of 30–50 % in the middle and high income countries and 80–100 % in low income countries [2,27,28]. Individuals may be infected with the virus for the first time (primary infection) or have a repeated infection (recurrent infection). The two serotypes do not cross protect but modify the response to infection with the other, hence an infection with a

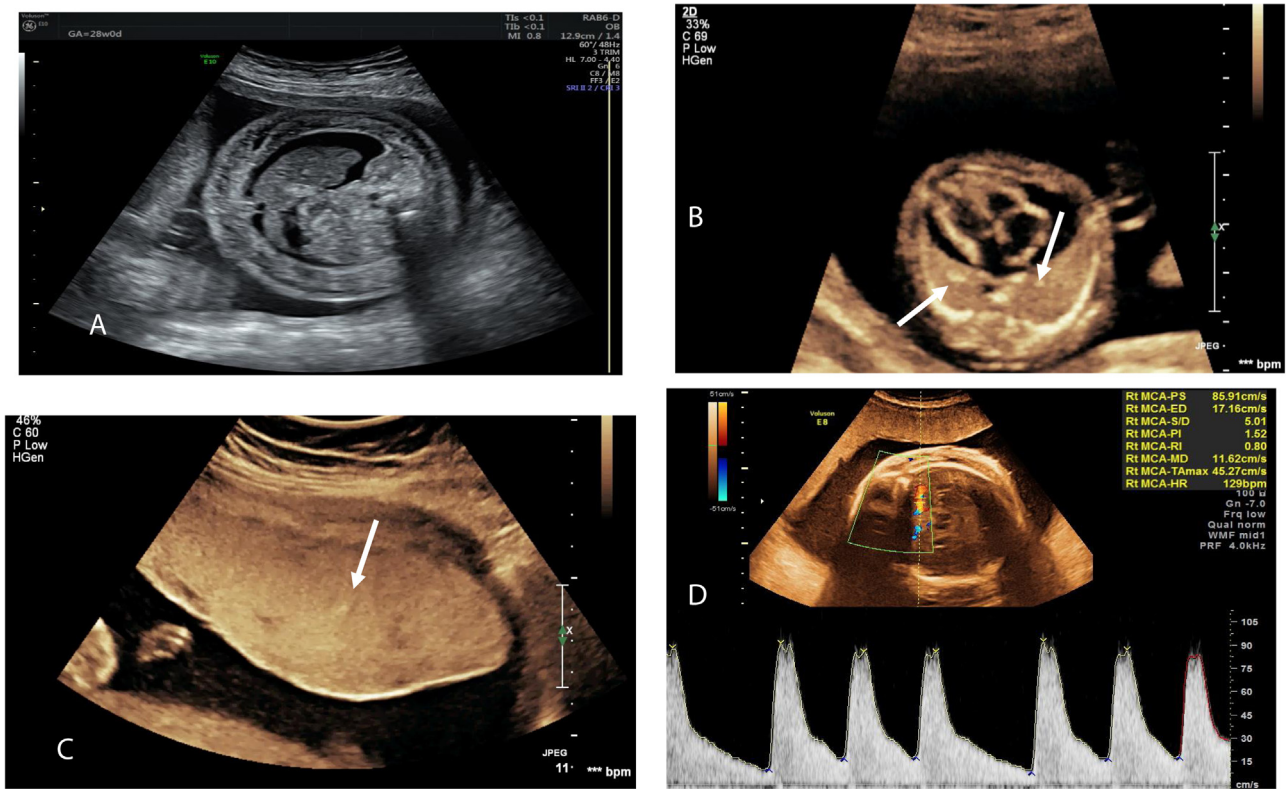

Fig. 3. 4 images of fetuses with intrauterine infection with parvovirus B-19. Fig. 3A shows a fetus with ascites and oedema around the abdomen, 3B shows a pericardial effusion and echogenic foci in the lungs (arrows) in a fetus with hydrops from Parvovirus, 3C placentomegaly with an intraplacental echogenicity (arrow)and 3D the middle cerebral artery Doppler with elevated PSV indicated of fetal anaemia.

different subtype in someone who has had an infection with the other subtype (referred to as non-primary first infection) is often not as severe as a primary infection (i.e. no prior exposure to HSV). When the infection occurs, it can be localised or disseminated. Disseminated disease is more common in those with a low immunity and if it does occur in pregnancy, it is more likely in the third trimester.

While HSV infections are common, the risk of vertical transmission during pregnancy is low. Most vertical transmissions occur during delivery when the fetus comes in contact with infected lesions on the genital tract or shed viruses in vaginal secretions. In symptomatic infected pregnant women, the risk of fetal infection has been estimated to be less than 1 % [29]. Although vertical transmission antenatally is rare, when it occurs, almost all the infected fetuses will exhibit abnormalities. These abnormalities which are very indistinguishable from those of congenital CMV include fetal growth restriction, hepatosplenomegaly, microcephaly, hydrocephaly, intracranial calcifications, periventricular and placental calcifications [27,28]. In the presence of these abnormalities with no obvious cause, maternal screening for both CMV and HSV should be considered. Factors which increase the risk of vertical transmission include the status of the fetal membranes (intact or breached), cervical infections, gestational age and transplacentally acquired antibodies [30] and cervical shedding. Shedding is less in those with recurrent infections hence the risk of vertical transmission in these individuals is much reduced. Fig. 4 shows placental calcifications in a case of HSV.

Infections acquired at the time of birth (90 %) or postpartum (10 %) present with neonatal HSV. It has been estimated that of the babies born through the genital tract containing one or more herpetic ulcers and thus shedding the HSV, about 30 % will develop neonatal herpes disease. If the fetus had acquired passive immunity through transplacental transmission of antibodies it is protected against infections acquired at birth as long as the serotype is similar to that for the antibodies [29,31].

The neonates who acquired the infection *in-utero* but who were not identified to have the infection may present with skin vesicles and scarring, eye disease, microcephaly or hydrocephaly [2]. Where the infection is acquired during delivery the clinical features appear at 3–5 days of life. The consequences of neonatal herpes are severe with up to 60 % of babies who develop herpetic disease dying and 20 % developing permanent sequelae including primary brain and eve damage [2,27,28].

Varicella zoster (chickenpox)

Varicella zoster (VZV) a DNA virus of the herpesvirus family that is highly contagious causes chickenpox infection, common especially in young children. Once infected, it tends to confer lifelong immunity although there are reported cases of reinfection but these are very uncommon [2,32]. In most high-income countries at least 80–90 % of the population are immune. During pregnancy, susceptible women who acquire the infection are at a greater risk of morbidity partly because of the impact of the physiological changes and depressed immunity [2].

Apart from the consequences of the infection on the mother there is a risk of vertical transmission with the virus causing severe malformations constituting the fetal varicella syndrome (FVS). The severity and variety of these abnormalities depend on the gestational age at transmission. The virus has a predilection for central nervous tissue. When vertical transmission occurs in the first trimester, the risk of malformation is 10–50 % [32–34]. When the infection occurs in the second and third trimesters the fetus is still at risk of malformations but the risk is similar to that of postnatal herpes zoster [32,33]. When fetal infection occurs in the last week of pregnancy it is associated with a perinatal death rate of 30 % [34].

The risk of FVS is approximately 0.5 % for infection in the first trimester (<13 weeks) and 2 % for infection between 13 and 20 weeks. If maternal infection occurs between 20 and 36 weeks of gestation, the risk of FVS is minimal although the CNS may still be affected. Maternal infection after 36 weeks, is, however associated with a 50 % fetal infection rate and a 25 % clinical varicella rate in the neonate [2,32].

The spectrum of fetal varicella syndrome may include polyhydramnios, limb deformities, skin scarring, fetal growth restriction, chorioretinitis, retinal calcifications, neonatal blindness and eye abnormalities, microcephaly, limb paresis, spinal cord atrophy, encephalitis, seizures and Horner's syndrome [2,32–34]. Fig. 5 shows some of the ultrasound and autopsy findings in fetuses with congenital VSZ. Suspected intrauterine infection is confirmed from amniotic fluid viral PCR. Such fetuses should be monitored serially by ultrasound scans not only for growth but to identify progression

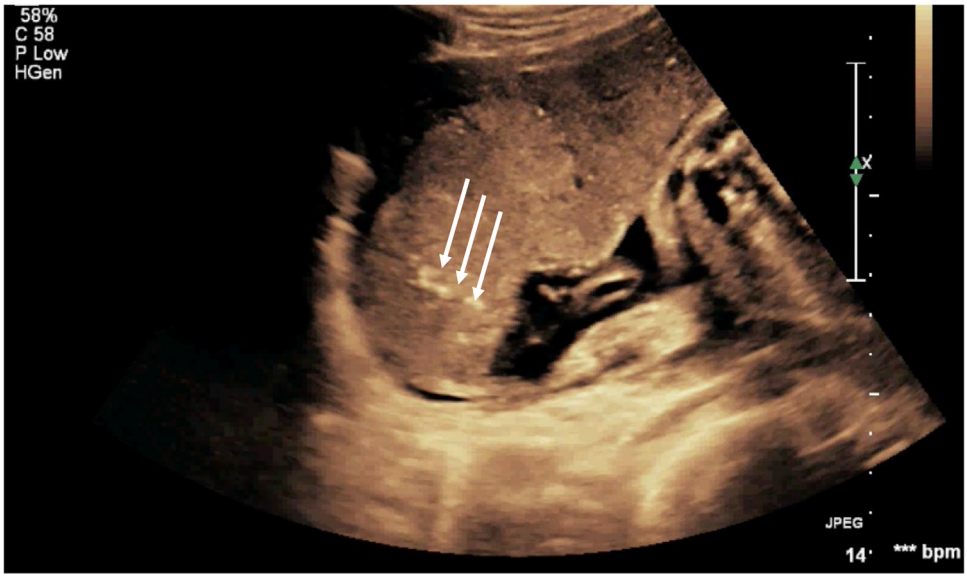

Fig. 4. Placenta from a pregnancy with intrauterine HSV infection showing placentomegaly and multiple echogenicities (arrows) within the placenta.

of abnormalities especially those in the cranium. Discussions on options including termination of pregnancy should be considered and discussed following ultrasound diagnosis of severe malformations such as microcephaly. MRI would be complementary in assessing severity of some of these malformations.

Zikavirus

Zikavirus (ZIKV) is a flavivirus, contracted through the bite of an infected mosquito specie known as *Aedes Egypti*. It has also been shown to be transmitted sexually. Infection from this virus is common in South America although it has been reported in other parts of the world [35]. Up to 80 % of those infected with the virus may have minimal or no symptoms. In the 20 % that have symptoms, these tend to be mild and self-limiting and include mild fever, skin rash, conjunctivitis, muscle and joint pain, malaise and headaches. The virus like most flaviviruses is also associated with the development of Guillain Barré syndrome [35].

Vertical transmission occurs during pregnancy and may result in a spectrum of malformations which have been grouped together as *congenital zika syndrome (CZS)*. The gestational age at vertical transmission influences the spectrum of abnormalities, with most occurring with vertical transmission in the late first and early second trimesters [1,36,38]. There are also reported abnormalities following infections in the third trimester, although these tend to be isolated. Infections in the late first trimester pose the greatest risk of CZS [36]. Included in the CZS are cranial morphology abnormalities (mainly fetal brain disruption syndrome or FBDS, consisting of severe microcephaly, overlapping cranial sutures, prominent occipital bones, redundant scalp skin in addition to severe neurological impairment) and brain abnormalities (most common of which is intracranial calcification, typically subcortical, unlike the periventricular calcification in congenital CMV), ocular anomalies (particularly microphthalmia and coloboma, cataracts and intraocular calcifications) and congenital contractures involving one or multiple joints (arthrogyrposis multiplex congenital or arthrogryposis, have all been reported in some cases). Infants of mothers with confirmed ZIKV infection born with a normal head circumference may still have underlying brain abnormalities. They should therefore be monitored postnatally for at least 12 months [36–42]. Fig. 6 shows some intracranial abnormalities associated with ZIKV infection *in-utero.* Amniocentesis for viral PCR will confirm intrauterine infection (especially in those with obvious abnormalities) but does not predict the risk of CZS. Termination of pregnancy, however, is an option that should be discussed in those with obvious abnormalities.

Other viruses

Infections in pregnancy with the viruses discussed above are those at the greatest risk of congenital malformations. Other viruses that may infect the mother, but may not cause severe or indeed any congenital malformations, could be associated with severe consequences in the neonate and for some of these a lifetime risk. Some of these viruses include Hepatitis B, HIV, Coxsackie, Influenza and Coronavirus [2]

Hepatitis B is an infection which is common world-wide with a carrier rate that varies with populations. The estimated chronic carrier rate world-wide is 5% (0.2 %–20 %) [43]. While fetal infection is uncommon, perinatal transmission is high with about 95 % of babies born to mothers who are carriers developing neonatal infection if they are not treated promptly after birth. Furthermore 85–95 % of these babies become chronic carriers, of which 25 % will progress to liver cirrhosis or develop hepatocellular carcinoma between the ages of 15 and 60 years [44]. In the rare event of intrauterine infection, there are reports of fetuses developing hepatosplenomegaly and intrauterine growth restriction.

HIV is not associated with congenital malformations but vertical transmission (>80 %) occurs during pregnancy especially in the last weeks of pregnancy and during childbirth. With appropriate anti-retroviral therapy, the risk is less than 1 % provided the viral load has been suppressed. The virus has been reported to cause placentitis, which may manifest on ultrasound as

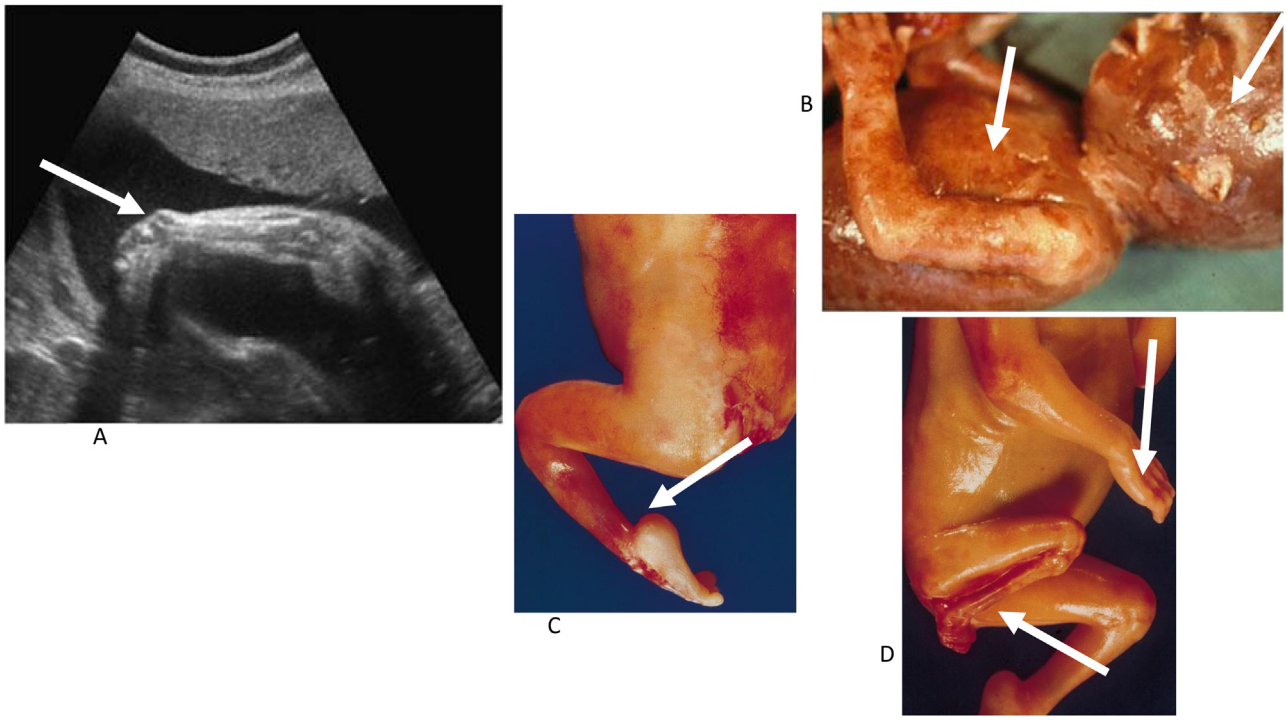

Fig. 5. Congenital VZV infection showing abnormalities – 5A limb abnormality, 5C-D autopsy findings with skin and limb abnormalities.

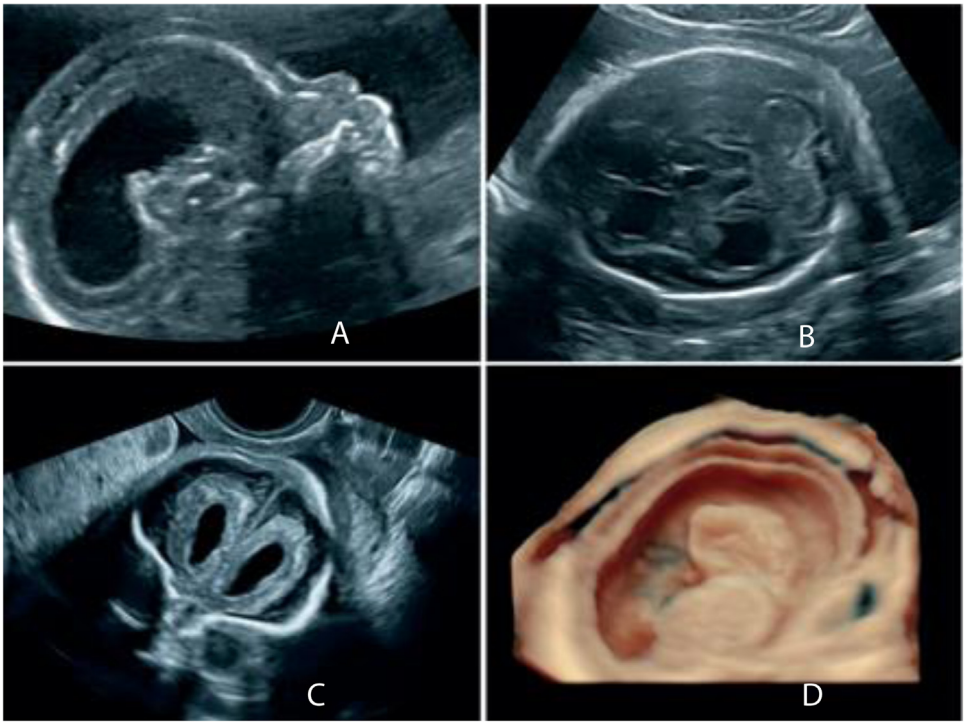

Fig. 6. Congenital Zika virus infection showing Ventriculomegaly, atrophy of the cerebral mantle, and enlarged pericerebral spaces observed by abdominal and vaginal ultrasound at different times during gestation (A) Parasagittal view with ventriculomegaly at 19 weeks of gestation. 6B-Axial view at 28 weeks of gestation. C6 - Coronal view (frontal lobe) showing the atrophy of the cerebral mantle at 23 weeks of gestation (case G). 6D-3D reconstruction of a parasagittal view at 18 weeks of gestation. Moderate bilateral ventriculomegaly was sometimes associated with a prominent third ventricle. CM = cerebral mantle. V = ventriculomegaly. V3=third ventricle. X = pericerebral space. *Courtesy of Schaub B et al. Ultrasound imaging for identification of cerebral damage in congenital zika virus syndrome: a case series. Lancet Child Adolesc Health 2017;1:45-55.*

an increased placental thickness (placentomegaly). The main risk to the fetus in women with HIV is often from co-infections with other viruses that are associated with severe teratogenicity such as CMV and HSV. It is recommended that when a diagnosis of congenital CMV or HSV is made, the woman should be screened for HIV as immunosuppression from this virus is associated with a greater risk of vertical transmission [45]. Equally important is management around the time of delivery and immediately after as most vertical transmissions occur intrapartum and during breastfeeding.

Coxsackie virus is an Enterovirus (a non-enveloped picornavirus) that causes meningitis, encephalitis, gastrointestinal disorders (especially diarrhoea), respiratory infections and in some cases paralysis. Most (up to 80 %) of those infected with the virus are asymptomatic but excrete the virus in throat secretions and faeces for weeks. Transmission rates are similar in symptomatic and asymptomatic individuals. Vertical transmission can occur in pregnancy and infections in the first trimester are associated with congenital malformations – typically involving the cardiovascular system, the gastrointestinal tract and the urogenital tract. Very rarely abnormalities have been described in the adrenals, liver and kidneys. These malformations are often as a consequence of focal necrosis.

Coronavirus is responsible for SARS-1, MARS and more recently SARS-2. This family of viruses cause severe and acute illness in a small proportion of those infected but there are no reported cases of congenital malformations. The MARS and SARS-1 infections are associated with a high rate of pregnancy loss but SARS-2 (COVID-19) has not been reported to be associated with an increase in miscarriages. Furthermore, there is no evidence of vertical transmission with any of these infections. The neonates may, however, be exposed to these viruses from an infected mother who is shedding the virus. Pregnant women with these viruses should be monitored with regular growth scans as the placentitis which has been described with COVID-19 for example may ultimately be associated with fetal growth restriction [46].

Protozoan infection

Toxoplasmosis

Toxoplasmosis is a protozoal infection caused by the obligate intracellular parasite of mainly domestic cats. It is acquired through eating infected undercooked beef, oocytes contaminated vegetables or drinking water contaminated with oocytes from cat litter. Just like CMV, a significant number of infected patients are asymptomatic. Symptoms are non-specific and include myalgia, flu-like features, body aches and fever. Susceptibility varies depending on the country of the individual as previous infection confers prolonged/lifelong immunity. In France for example 70 % of the population are immune with only 30 % susceptible compared to the UK where susceptibility is over 70 % [47–49]. The incidence of maternal and neonatal infections varies from country/region to another but rates reported in France are 3–4/10,000 live births [50].

Vertical transmission occurs in pregnancy during an acute infection when there is parasitaemia. The transmission rate is

Table 2
Rates of vertical transmission and of severe disease at each trimester.

Trimester	Risk of congenital infection (%) with CI in brackets	Risk (%) of developing severe disease (CI in brackets)
1–13 weeks	6 (3–10)	61 (34–85 %)
14–28 weeks	40 (33–47)	25 (18–33)
29–42 weeks	72 (60–81)	9 (4–17)

highest in the third trimester. Table 2 shows the vertical transmission rate with each trimester as well as the risk of severe consequences following the transmission. While transmission is greatest in the third trimester, the risk of severe disease to the fetus is very low, whereas in the first trimester the risk of vertical transmission is 6–10 % with a 60 % risk of severe consequences [47–49].

The spectrum of abnormalities that are identifiable on ultrasound scan include calcifications in the abdomen especially the liver, hepatosplenomegaly, fetal growth restriction, hydrocephaly with ventriculomegaly, periventricular calcifications, bilateral chorioretinitis, placentomegaly and hydrops [47–49,51,52]. Fig. 7 shows some of the features of toxoplasmosis infection in the fetus that can be identified on ultrasound scan. Prognosis of affected fetuses can be gauged from the degree of ultrasound abnormality and where possible this should be complemented with MRI. Intrauterine infection can be confirmed from PCR on amniotic fluid obtained from those with clinically confirmed infections or with fetuses with abnormalities highly suspicious of congenital toxoplasmosis. Treatment of the mother with a combination of sulphadiazine, pyrimethamine in combination with folinic acid has been shown to reduce the sequelae in the fetus but is not as effective as spiramycin (which does not cross the placenta hence has no effect on fetal infections) in treating maternal disease, and in turn may reduce vertical transmission.

Bacteria infection

Syphilis

Syphilis is caused by the bacterium *Treponema pallidum,* a spirochaete sensitive to penicillin. It is estimated to have a prevalence of about 15/100000 resulting in approximately 2 cases of congenital syphilis per 100 cases of either primary or secondary disease in women of reproductive age [51]. Vertical transmission occurs during pregnancy irrespective of the stage of the disease (primary, secondary or tertiary). In pregnant women with untreated primary, secondary and tertiary syphilis the fetal infection rate is respectively approximately 100 %, 90 % and 30 % [2,53]. Treatment of the mother significantly reduces the risk of vertical transmission.

The bacteria infect the placenta and on entering the fetus cause a spirochaetemia with widespread dissemination of the bacteria in all organs where it can cause severe consequences. The congenital spectrum of malformations includes unexplained stillbirth, hepatosplenomegaly, skin lesions and destructive bony tissue features (saber shin, celery stalk), encephalitis, chorioretinitis, bone deformities and endocarditis. Perivascular cuffing may be found deep in the tissues of the central nervous system [53–55].

The neonate with congenital syphilis who is a liveborn may have hepatosplenomegaly with jaundice, multiple bone involvement, snuffles, haemolytic anaemia and pneumonia. The stillborns are commonly macerated, with protuberant abdomens and bullous vesicular skin lesions containing a large number of treponemes. The hepatomegaly is usually associated with fibrosis and persistent extramedullary haematopoiesis. Occasionally there will be deposition of the antigen-antibody complex on glomeruli causing renal injury. When the brain is involved, changes are commonly found in the meninges around the brainstem and the optic chiasma. Other consequences include syphilitic endocarditis, osteochondritis, periostitis and osteomyelitis. The hydrops fetalis that results in cases of congenital syphilis is secondary to fetal anaemia [54–56].

The placenta in cases of congenital syphilis is abnormally thick but not oedematous. The placental-fetal ratio is commonly at least 0.5. Focal villitis causes vascular changes including endothelial proliferation and perivascular inflammation - all of which affect effusion and therefore fetal growth restriction. The most likely abnormalities to be found on ultrasound scan are growth restriction and a thickened placenta. Some of the pathologies in the central nervous system may also be obvious on ultrasound as well [56]. Fig. 8 shows an abnormality that may be obtained from ultrasound scan.

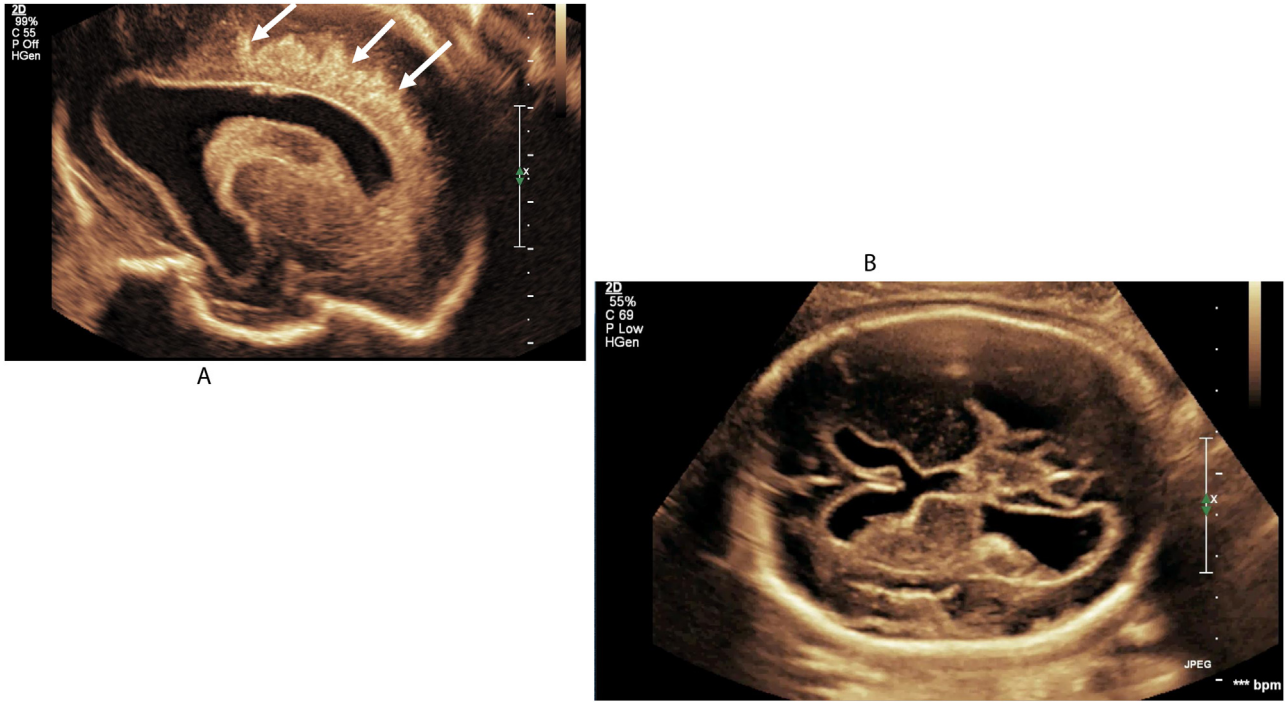

Fig. 7. Congenital toxoplasma gondii infection. 7A showing Echogenic nodular foci identified by the arrows in a fetus with congenital *Toxoplasma gondii* infection and 7B showing ventriculomegaly.

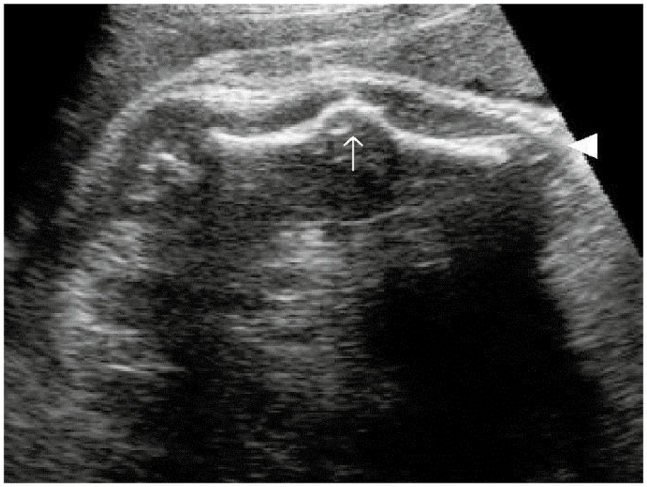

Fig. 8. Congenital syphilis showing an affected fetal bone. *Courtesy of Bailão et al. Ultrasound markers of fetal infections Part 2. Ultrasound Quarterly 2006;22:137-151.*

Conclusion

Intrauterine infections are common and in most cases are asymptomatic. A significant number of viruses and bacteria have a dual effect – on the mother and the fetus or neonate. The effect of these infections on the fetus depend on their teratogenicity and the gestational age at which vertical transmission occurs. Most of those that cause malformations are infections in the first trimester. Congenital malformations vary from mild and clinically insignificant to those severe enough to have a major impact on the fetus/neonate. For most of these infections, a high index of suspicion is required based on identification of abnormalities associate with the infections and timed investigations such as amniocentesis. Management must take into consideration the impact of the infection and resulting malformations on the outcome for the fetus as well and the legal/statutory requirements for the country.

Declaration of Competing Interest

The authors report no declarations of interest.

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