USG Role in Perinatal Infection

Alaa Ebrashy

ABSTRACT

Prenatal diagnosis can aid the obstetrician in evaluating a mother with suspected infection that can be transmitted to the fetus. The ultrasound (US) can exclude or identify anatomical defects of fetal heart, brain, detect thoracic or abdominal lesions, evaluate the liver and spleen volume, determine the degree of hemodynamic disturbance and suggest anemia. Congenital infections present with a wide spectrum of US markers and lesions, it may present as early pregnancy loss, nonimmune hydrops fetalis (NIHF), fetal growth restriction, CNS lesions, cardiothoracic lesions and lesions of the GIT.

Role of US-guided invasive procedures in fetal infections includes amniocentesis-chorionic villus sampling, percutaneous umbilical blood sampling.

Keywords: Ultrasound, Intrauterine or perinatal infection, Toxoplasmosis, Cytomegalovirus, Parvovirus.

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INTRODUCTION

There are two situations where the obstetricians might need to know the role of ultrasound in perinatal infection. The first situation is that when the pregnant lady reports to her doctor that she has a rash, she is exposed to infection by getting near to a diseased person, she did some investigations raising the suspicion of being attracted infection during pregnancy, etc. In all these conditions the main question is: how could she know that her baby is safe, can ultrasonography (USG) give a clue to this question?

The second situation is that during a routine fetal USG examination, doctor is encountered with some fetal abnormalities that could be related or not to intrauterine infection.

In order to be ready in both situations you should:
- First, know a brief knowledge about each organism that cause intrauterine infection and how could it be detected by USG
- Second, what are the USG signs that should arouse your suspicion for intrauterine infection.

How to detect, when to detect, modalities of diagnosis, with major emphasis on ultrasound is what will be covered in this chapter.

First, we start with the general ultrasound features of perinatal infection, the role of invasive tests in their diagnosis.

Second, we shall discuss in brief each organism separately together with its USG signs that could be present in case of infection.

ULTRASOUND FEATURES IN CONGENITAL INFECTION

Intrauterine infection can present with a wide spectrum of USG markers and lesions depending on the type of the organism and the age of pregnancy at which the mother contracted the disease and above all the time between acquiring infection and USG examination.

Characteristic ultrasound markers in a mother with a positive TORCH (Toxoplasmosis, other agents, Rubella, CMV, Herpes simplex) screening test have a high predictive value for congenital infection and may have prognostic significance.

Among these markers we can mention early pregnancy loss, nonimmune hydrops fetalis (NIHF), intrauterine growth restriction, cranial lesions, cardiothoracic lesions, gastrointestinal lesions and other lesions.

Early Pregnancy Loss

Defined as a miscarriage within the first 12 weeks of pregnancy. Infection is considered a rare cause of early pregnancy loss.[1] Among these organisms are *Toxoplasma gondii*, cytomegalovirus (CMV) and parvovirus B19 (PVB19). The USG suggestive of the occurrence of early pregnancy loss include fetal bradycardia, discrepancy between the gestational age and crown-rump length. Definite diagnosis depends on the demonstration of an empty sac of more than 15 mm by transvaginal sonography (TVS) and embryo with no pulsations documented by Doppler.[2] There is no any recent evidence suggesting that infection could be related to repeated abortion.

Nonimmune Hydrops Fetalis

Hydrops fetalis represents a specific condition characterized by an increase of total body water content. In such a condition, the excess fluid collects by ultra filtration in body cavities (pleural, pericardial and peritoneal effusions) and/or in the subcutaneous tissue. Placental edema and polyhydramnios are frequently associated (30-70%). By definition, the term NIHF refers to fluid collections in at least two body cavities or to one fluid collection plus diffuse subcutaneous edema.

ETIOLOGY AND PATHOGENESIS IN INTRAUTERINE INFECTION

The NIHF is a nonspecific sign of various infections vertically transmitted from mother to fetus, including both viral and nonviral infections.

Severe hemolytic anemia or aplastic anemia that can precipitate heart failure is often the primary cause.[3]

In the case of viral infections, the etiology is probably due to different and synchronous mechanisms: inflammation, myocarditis with pump deficit as in coxsackievirus B or a major cardiac structural defect secondary to a rubella infection during the first trimester. Toxoplasmosis may cause NIHF possibly due to excessive extramedullary hematopoiesis with portal hypertension secondary to liver congestion.

PVB19 is tropic to rapidly diving cells in particular the bone marrow red cell precursors causing hemolysis and aplasia of the bone marrow.[4]

The pathophysiology of NIHF in cases of CMV or *T. pallidum* is less clear and could be due to combined effect of anemia and hepatic dysfunction resulting in hypoprotinemia and portal hypertension. The viruses most frequently associated with fetal hydrops are PVB19, coxsackievirus, herpes virus (Varicella), CMV, adenovirus and influenza virus type B. Among the nonviral infections, the most common are syphilis, listeriosis and toxoplasmosis.

The final result of the various conditions mentioned above is a breakdown of equilibrium between intracapillary and extracapillary pressures, with consequent fluid ultra filtration in the interstitial space.

The NIHF due to fetal infection can occur anytime in pregnancy but more common in second- and third- trimester. The fluid collections in the abdomen, pleura or pericardium appear as sonolucent areas with different shapes characteristic of the different locations. Subcutaneous edema appears as a moderately hyperechoic thickening of the soft tissue of the fetal face, trunk and sometimes limbs, the fluid collection may be limited to one or two sites and therefore its diagnosis needs dedicated planes. Axial views of the head, neck and thorax may allow assessment of the extent and severity of the effusions and the subcutaneous edema. With regards to the ascites, it should be noted that initially the fluid collects in the pelvis only and therefore it should be sought in this region and not at the level of the liver.

Intrauterine Growth Restriction

It is also a nonspecific feature of most congenital infections. It is a more common in rubella, CMV and *T. pallidum*.[5] It also has some relationship with varicella-zoster, HIV and Malaria. The IUGR in cases of intrauterine infection may be explained on the ground of capillary endothelial damage during organogenesis, which in turn induces a decrease in the number of cells having a cytoplasmic mass within the normal range together with a cytopathic effect. When the infection is transmitted to the fetus in the first trimester, the IUGR will be a manifestation of the second trimester USG usually severe symmetrical pattern and associated with oligohydramnios in most cases hence the fetal anatomy could not be well appreciated. In any case showing symmetrical IUGR early in the second trimester, infection should be always considered and TORCH test is therefore always be performed.[6]

Cranial Lesions

The most common cranial lesions secondary to fetal infection is seen by are cerebral echogenic foci (calcifications), ventriculomegaly (Fig. 1), microcephaly and hydrancephaly. A fetal infection should be suspected when ventriculomegaly is associated with hyperechogenic foci and periventricular cysts.

These lesions are both inflammatory (Gliosis) and destructive lesions. The most common organism that causes cerebral lesions is CMV and less commonly *T. Gondii*. The ventriculomegaly that may be seen in such cases is the consequence of aqueductal obstruction. Hydrancephaly observed in cases of congenital infections, such as toxoplasma and CMV can be explained on the basis of causing necrotizing vasculitis with consequent destruction of the cerebral tissue.[7]

The addition of magnetic resonance imaging (MRI) increases the positive predictive value for diagnosis of fetal brain abnormalities with CMV.[8]

Fig. 1: Ventriculomegaly

Eye Lesions

Eye lesions seen in congenital infection include congenital cataract, micro-ophthalmia and chorioretinitis. They are observed mainly with congenital rubella and congenital toxoplasmosis.[9]

Cardiothoracic Lesions

Congenital heart defects mainly as pulmonary valvular stenosis and ventricular septal defect are among the clinical features of congenital rubella syndrome. Similar defects have occasionally been observed following first trimester congenital CMV or toxoplasmosis infection. Cardio-myopathies, such as endocardial fibroelastosis (interstitial myocarditis) have been linked to coxsackievirus B and to adenovirus and PVB19.[10] Major heart anomalies are usually complicated by NIHF. Pleural effusion may represent an early stage of NIHF and may be associated with a major fetal infection usually the heart. Isolated pleural effusion is rarer and has only been observed in one case of adenovirus infection[11] and one case of PVB19 infection.[12]

Gastrointestinal Lesions

Most congenital infections show abnormal features of the liver, spleen and bowel on USG. The most common sonographically detected markers are peritoneal hyperechogenicities and/or hyperechogenic bowel which have been described mainly within the context of congenital CMV, HSV, VZV and PVB19.[13] True parenchymal liver or splenic hyperechogenicities are far less common and have occasionally been related to congenital infection.[14] The pathophysiology of these echogenicities is unclear. Focal lesions are probably secondary to localized ischemia or

inflammatory reaction with calcification of the tissue, diffuse bowel hyperechogenicity could be due to thickened meconium. Congenital infections due to PVB19, CMV, *T. pallidum* or toxoplasmosis may be associated with ascitis and hepatosplenomegaly (Fig. 2). These anomalies are secondary to direct infection of the fetal liver parenchyma with secondary enlargement and progressive alteration of liver function.[15] Ascitis can be detected by USG even there is less than 50 ml of intraperitoneal fluid and can be the first presenting sign of congenital infection. Small amounts of ascitis are best visualized at the edge of the liver and may be seen to gradually outline the liver. In severe cases USG picture of the fetal abdomen show free floating or compressed bowel loops. Ascitis is often is early manifestation of serous fluid accumulation in fetuses who later develop full blown hydrops. Intrauterine fetal infections are among the most common causes of hepatomegaly, CMV infection, when severe is commonly associated with hepato-splenomegaly (Fig. 3). Fetal infections are also the primary cause of splenomegaly with or without hepatomegaly. In particular, CMV infection, when severe is typically associated with splenomegaly, as well as hepatomegaly and ascites. If the enlargement of the spleen and/or liver is severe, the diagnosis of these conditions is straightforward, the two organs occupying most of the abdomen. The recognition of hepatomegaly and splenomegaly is made even simpler if ascites, which acts as an intra-abdominal contrast medium, is associated. If hepatomegaly is very pronounced, the prominence of the liver pushes the anterior abdominal wall, causing a dip at the thoracoabdominal junction, similarly to what happens in cases of severe thoracic hypoplasia, although in this case it is the abdomen

Fig. 2: Hydrops hepatosplenomegaly

Fig. 3: Hydrops splenomegaly hepatomegaly

that is enlarged rather than the thorax that is hypoplastic. Nomograms of the maximum diameters of the liver and the spleen have been published. Then 3D ultrasound also have recently been used for estimation of liver and spleen volumes *vs* gestational age.[16]

Other Lesions

Placental edema and enlargement is commonly found specially in cases of NIHF as in CMV and toxoplasmosis.[16] Urogenital tract lesions have occasionally been reported in cases of CMV and toxoplasmosis. Limb defects have been rarely observed in congenital VZV.

What is the Role of Invasive Procedures in the Diagnosis of Intrauterine Infection

There are three modalities of invasive procedures for the diagnosis of fetal infection namely amniocentesis, chorionic villus sampling (CVS) and cordocentesis.

The CVS can be done after 11 weeks and have been used in particular for first trimester rubella. Its main disadvantage is early diagnosis which may be useful when there is maternal serological evidence of infection early in pregnancy however this method poses a theoretical risk to the fetus as it damages the placental barrier, which may result in an increased transfer of viral particles or parasites to the fetus.[17]

Cordocentesis is played a key role in the diagnosis of most common congenital infections in the 1980s and early 1990s. No fetus with a documented infection has a completely normal hematological profile [5] white blood count total and differential, TORCH specific IgM, fetal liver enzymes measurement, all can be assessed in cases of infection. However, with the development of polymerase chain reaction (PCR) analysis on the amniotic fluid, its role in this context is fading.[5]

The only advantage of cordocentesis is in cases of PVB19 infection in which the fetal hematological profile is crucial in the management of these cases.

We left with the amniocentesis which is now the most common invasive procedure used for diagnosis of fetal infection.[17] The PCR is now the preferred method for analysis of the amniotic fluid in cases of fetal infection. The development of quantitative PCR analysis has optimized the specificity of this assay, preventing the false-positive results that were seen with the earlier qualitative PCR analysis. Current studies in case of CMV are now trying to correlate viral load and degree of fetal damage.[18] An essential point to be mentioned here is the timing for amniocentesis to avoid false-negative PCR results delays of more than 5 to 6 weeks between the serological diagnosis

of maternal CMV and toxoplasmosis infection and the invasive procedure are recommended to increase the sensitivity of prenatal diagnosis.[19]

PRENATAL MANAGEMENT OF SPECIFIC CONGENITAL INFECTIONS USING ULTRASOUND MARKERS AND INVASIVE PROCEDURES

Cytomegalovirus

Cytomegalovirus is found universally throughout locations and is species specific. Seroconversion occurs in approximately 1% of pregnant women in UK, more than 2% in other European countries and the USA.[20]

Primary CMV carries a high mother to fetus transmission rate ranging from 25 to 40% regardless of the stage of pregnancy.[21] In secondary recurrent infection, the transmission rate is much lower almost 5%.[19] Overall congenital CMV infection is asymptomatic at birth in 90% of infants infected *in utero*.

The classic triad of blood dyscrasia (petechiae and thrombocytopenia), IUGR and chorioretinitis is uncommon less than 10% *in utero* or at birth. Among the ultrasound markers for CMV infection that could be detected are cranial calcification periventricular in position without shadowing, ventriculomegaly, echogenic bowel (Figs 4 and 5), enlarged liver and spleen, focal calcification in the liver and mild ascitis, severe IUGR. Placentomegaly (Fig. 6) is noted in 32% of the time. Those cases showing cerebral manifestations and/or severe IUGR are more prone to develop neurological sequel.[22,23]

The mere detection of positive IgM and IgG is not indicative of active infection unless we obtain a rising titer within 2 weeks since the IgM could persist in the circulation for more than 18 months from last infection.[23] Differentiating between primary or secondary infection is somewhat important for assessing the possibility of fetal infection as mentioned earlier. The CMV IgG avidity test is very useful in this domain.[24]

Intrauterine infection diagnosis could be achieved through amniocentesis and isolation of the CMV DNA by PCR with a sensitivity of 80 to 99% of cases.[17] It should be noted that it takes 5 to 7 weeks after fetal infection for viral replication in the fetal kidneys to be present in sufficient quantity to be secreted into amniotic fluid, also the PCR testing is unreliable prior to the 21st weeks of pregnancy. This means that amniocentesis for CMV detected by PCR should not be performed before the 21st weeks and with an elapse of at least 5 weeks from the time of maternal infection.[19]

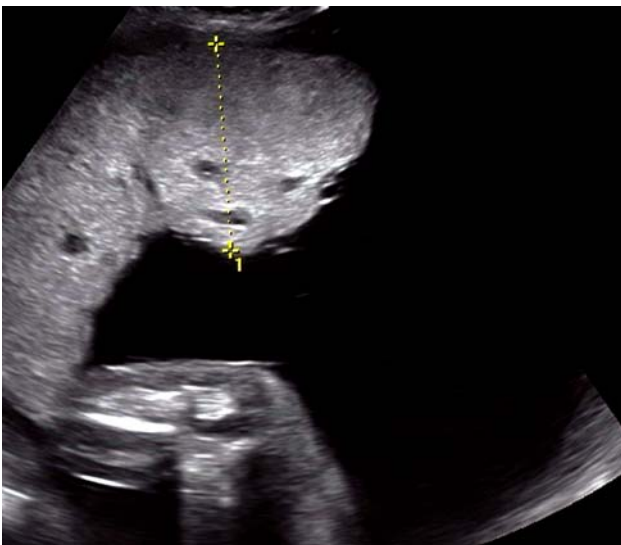**Fig. 4:** Echogenic bowel

Fig. 5: Hydrops e-bowel

Fig. 6: Placentomegaly

Treatment of CMV Infection

There is currently no approved treatment for congenital infection. Gangciclovir being effective treatment for CMV

however not safe in the first trimester.[22] Valaciclovir is showing some promise for use however with limited research till now.[25] Hyperimmunoglobulin appears to be an effective drug for fetal however also with limited data.[22]

Toxoplasma

Mode of Infection

It is caused by the protozoon, *Toxoplasma gondii*. The definitive host is the cat and the intermediate hosts include humans, numerous mammals and birds which acquire the infection from the oocysts contained in cat feces and thus seronegatives are urged to avoid contact with cats, wash fruits and vegetables thoroughly and avoid raw meat.[26]

Transmission

The rate of mother to fetus transmission depends on the gestational age and the time of the initial infection. It is around 15%, 30% and 60 to 70%, in the first, second and third trimesters respectively. However, the reverse is the situation for the severity of infection, being highest in first trimester and almost nil in the third trimester.[27]

Ultrasound Signs

The main ultrasound sign of prenatal toxoplasmosis infection is ventriculomegaly, intracranial calcification (Fig. 7). Choroidoretinitis is among the sequelae detected postnatal. Other ultrasound markers include hepatospleno-megaly, ascitis.[15]

Testing

If the serologic testing shows that the woman has contracted toxoplasmosis during pregnancy by a positive IgG and IgM with a rising titer, detecting *T. gondii* in the amniotic fluid by PCR through amniocentesis is the preferred methods for assessing fetal infection with a sensitivity more than 80% and specificity of 96%.[28,29]

Treatment

Spiramycin can decrease the risk of congenital toxo-plasmosis by around one half. It is taken as 1g every 8 hourly and is continued until delivery.[30]

This drug does not cross the placenta, so in the evidence of fetal infection by amniocentesis and PCR, treatment should be in favor of other drugs that are effective and also cross the placenta.[30] This include both pyrimethamine and sulfadiazine. Different regimens are used, however, in all of them folic acid is added as both of them are folic acid antagonist.

Examples are: pyrimethamine 50 mg/day + sulfadiazine 1 tid + folinic acid 10 to 25 mg/day for 3 weeks alternating

Fig. 7: Cranial calcification

with 3 weeks of spiramycin 1 gm tid. This regimen is continued until term.[30,31]

Parvovirus B19 Infection

It is caused by the human parvovirus B19 which belongs to the parvoviruses group a single DNA strand.[32] The viruses affect the function of the hematopoietic organs through the infection and lysis of erythropoid cells. The disease is very mild for the mother and carries a 33% placental transmission rate following maternal seroconversion at any stage of pregnancy. The virus can cause severe destruction of erythroid progenitor cells in the fetus with the risk of developing fetal anemia, hydrops and intrauterine death.[32]

Transmission

It would lead to fetal anemia in 7 to 17% of affected cases. It is not associated with a clinically significant risk of malformations.[32]

Ultrasound Signs

The hallmark of this infection is fetal hydrops which may be severe in very low hemoglobin levels. It accounts for 10 to 15% of nonimmune fetal hydrops NIHF.[33,34]

Testing

Nonimmune hydrops should call for a parvovirus B19 IgG and IgM antibody testing in the maternal serum. In 80% of the cases, the virus can be detected in the fetal blood by PCR. In case of NIHF the evaluation of middle cerebral artery peak systolic velocity is an important tool to diagnose and follow-up fetal anemia.[35,36] This should be followed

by cordocentesis and intrauterine blood transfusion which is the only way for fetal survival, more than 80% of the fetuses transfused *in utero* will survive.

Varicella Zoster

DNA virus of the herpes family responsible for chicken pox (varicella), the primary infection and herpes-zoster shingles, a reactivation of the virus occurring at any age but with an increasing incidence in adulthood transmission via droplet infection and infection is followed by long lasting immunity.

Both maternal and fetal infection is important and serious. Pregnancy increases the risk of disease associated complications particularly in late pregnancy. Pneumonia occurs in up to 10% of cases and could be so severe that it necessitates mechanical ventilation.[37] Fetal varicella syndrome occurs when the fetus is infected during maternal viremia in the first 20 weeks of gestation. The risk of fetal varicella syndrome is estimated to be 0.4% in the first 12 weeks of pregnancy, 2% between 13 and 20 weeks of gestation, the syndrome does not occur if maternal infection occurs after 20 weeks.[37]

Prenatal diagnosis of fetal varicella syndrome depend on serial USG examination 5 weeks or later after primary infection among the signs are polyhydramnios, microcephaly, liver calcification (Fig. 8), NIHF, limb hypoplasia. Varicella embryopathy is the term used for infants contracted the infection intrauterine.[37] It comprises cutaneous scars, denuded skin, limb hypoplasia, muscle atrophy and rudimentary digits, other more frequent abnormalities are microcephaly, intracranial calcification cortical atrophy, cataract, chorioretinitis, micro-ophthalmia and psychomotor retardation.

Fig. 8: Liver calcification

MANAGEMENT

Exposure before 20 Weeks

If the mother is not immune: I. globuline 1000 gm IM may be given. If she develops chickenpox, council her for the possibilities of fetal infection and follow-up by serial USG.

Exposure after 20 Weeks

There is no fetal infection in these cases, however, the mother may develop some complications mainly pneumonitis, thus if she is presented within 24 hours of chickenpox rash. She may be given oral acyclovir 800 mg 5 times daily for 7 days to reduce the severity and duration of illness. If presented after 24 hours, the acyclovir is of no effect and just follow-up the disease progression.[38,39] In herpes-zoster, the fetus is unaffected by maternal herpes-zoster unless mother is immunosuppressed.

Rubella

Mode of Infection

It is caused by a small RNA togavirus, the rubella virus.

Transmission

Direct contact with infected droplets. If the infection is contracted in the first 6 weeks of gestation, two-thirds of the fetuses will develop a rubella syndrome. Infections in later weeks are associated with lower risks, 25% between 7 and 9 weeks, 20% between 10 and 12 weeks and 10% between 13 and 17 weeks.[40]

Ultrasound Signs

The anomaly typically found in rubella embryopathy is ventricular septal defect (VSD) or tetralogy of Fallot. Additional signs include growth retardation and microcephaly. The triad of cataract, cardiac anomalies and deafness (Gregg syndrome) is a classic embryopathy caused by the infection.[15]

Testing

A normal ultrasound scan cannot exclude fetal rubella infection, thus in cases of primary rubella infection, it is possible to detect the virus in chorionic villi or amniotic fluid. Cordocentesis has reasonable accuracy but should not be performed earlier than 22 weeks since the IgM production may still be too low before 21 weeks. A good strategy in earlier cases is to start with CVS or amniocentesis and if negative, confirm the result by cordocentesis at 22 weeks.[41]

CONCLUSION

- Ultrasound markers of a congenital infection include echogenic bowel, hepatosplenomegaly, NIHF, cranial anomalies mainly hydrocephalus and cranial calcifications and early symmetrical IUGR.
- Maternal screen for TORCH and TORCH-like infections is recommended in these cases.
- Serial ultrasound should be performed every 2 weeks in pregnancies at risk for congenital infection as in case of exposure to infection or maternal seroconversion.
- Amniocentesis is considered the standard invasive test for the diagnosis of most intrauterine infection where isolation of the virus is done by PCR with a sensitivity now approaching 100%.
- Intrauterine infection are not a cause for recurrent pregnancy loss, so TORCH is not indicated in these cases.

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ABOUT THE AUTHOR

Alaa Ebrashy

Professor, Department of Obstetrics and Gynecology; Director of Fetal Medicine Unit, Cairo University, Giza; Board Member of WAPM International Committee; Board Member of the Fetus as a Patient Society; Clinical Director of Ian Donald School, Egypt
e-mail: ebrashy3@yahoo.com