In clinical practice the foetal-maternal infectious diseases are both common and potentially severe, but screening policies vary greatly among different nations reflecting different perceptions of the relevance of a specific infection.

However, progresses in immunological and ultrasound techniques and foeto-maternal therapies have made prenatal diagnosis of congenital infections one of the least established areas in foetal medicine. Combined use of non invasive (ultrasound) and invasive (amniocentesis, funicolocentesis) protocols allows us to suspect or exclude a foetal involvement in the majority of cases.

Notwithstanding these progresses, several aspects of materno-foetal infections and foetal damages and/or sequelaes have to be clarified. The frequency of a specific infection during pregnancy and the transplacental passage rate for each gestational age are often unknown. The evidence of a maternal infection does not imply foetal infection, and, on the other hand, the foetal involvement does not automatically imply damages or long term sequelaes. This issue is further confused by several variables which interfere with the natural history of congenital infections.

The diagnosis of foetal infection is even difficult. Assay of total or agent-specific foetal IgM is unreliable before 20 weeks of gestation, due to the foetal immune system immaturity, and later in gestation can cause underestimation of real incidence of foetal infection.

Polymerase chain reaction can detect the presence of an infectious agent’s genome but, for its high sensitivity, is prone to relatively high false positive rates from maternal or environmental contamination, or false negative if the strains exhibit significant genetic variability.

Isolation or culture of the infectious agents from foetal tissue is crucial to calculate the time elapsed between maternal infection and testing: slow growing viruses can require several weeks to spread to the foetus and to be excreted in the compartment being tested. On the other hand, if foetal blood is collected, during a transitional phase in the cycle of the infectious agent, the signs of viraemia may be missed.

Finally, the foetal response and involvement to an infection is strictly dependent both for the agent and the gestational age at the time of infection.

Ultrasoundography plays a pivot role in the suspect and/or diagnosis of foetal infection, as foetal infectious agents can produce a wide spectrum of ultrasonographic abnormalities, that may be the first clinical sign of foetal infection in patients with a negative clinical history [1]. Ultrasoundography has also a primary role in the intrauterine follow up of infected foetuses. The finding of a single foetal abnormality, e.g. an intrahepatic calcification not associated with a hepatic mass or lesion, must induce a ultrasonographic follow up because some foetuses may later develop further signs of infection [2].

Unfortunately, no ultrasonographic findings are clearly pathognomonic for a particular agent, so the ascertainment of a foetal infection must be done, if any abnormality suggestive of infection is noted, even in case of a negative clinical history. However, the evidence of the foetal ultrasonographic expression of a specific infectious agent can help us to individualize the diagnostic process and to earlier define the prognostic significance of a single or multiple abnormalities.

ULTRASONOGRAPHIC SIGNS OF FOETAL INFECTION

As stated above, the foetal response to an infection is dependent both on the agent and gestational age at the infection time. However, the different foetal infectious diseases can show similar anatomopathological and clinical characteristics, as the TORCH acronym [3] indicate affinity among similar clinical manifestations from different infectious agents. This concept has been recently overwhelmed [3]; however, several ultrasonographic features are similar among different clinical findings.
A percentage between 10 and 15% of intrauterine growth retarded (IUGR) fetuses is etiologically connected with intrauterine infection. IUGR due to foetal infections are generally symmetric, or low profile. In some cases, as cytomegalovirus infections, the cerebral involvement with microcephaly can generate an “inverse asymmetrical” IUGR; in other cases, as toxoplasma and Syphilis, the placental involvement can cause a reduction in placental function and a foetal “brain sparing effect”, with the development of a asymmetrical or late flattening IUGR.

Ventriculomegaly is defined as a dilatation of lateral ventricles posterior horns. The currently accepted cut-off value is 1.0 cm [4] and appears to be invariant in respect to gestational age.

Periventricular calcifications can be seen as small areas closely to periventricular wall, hyperechogenic [5], but very difficult to identify by ultrasound for calcification flecks too small to cause acoustic shadowing.

Microcephaly is featured by a typical disproportional size between skull and face. The forehead is sloping, the brain is small with the cerebral hemispheres affected to a greater extent to diencephalic and rhomboencephalic structures.

Many difficulties arise in attempting to identify foetal microcephaly. The utility of head measurements alone may be hampered by incorrect dating or concomitant IUGR. A comparison of biometric parameters, such as the head circumference/abdominal circumference ratio and the femur length/biparietal diameter ratio has been suggested. Nevertheless, both false positive and false negative diagnoses occur frequently [6]. A qualitative evaluation of the intracranial structures is very useful if adjuncted to biometry. In fact, the microcephaly due to viral infections is often associated with morphologic derangement, particularly with ventriculomegaly [7].

Fetal hepatic calcifications are an uncommon finding in pregnancy (about 1 on 1,750 pregnancies, [8]) and can be categorised, according to their location, namely, peritoneal, parenchymal and vascular.

A foetal infection can cause single or multiple foci of parenchymal calcifications: usually, the ultrasonographic appearance is a randomly scattered nodular calcified area. The differential diagnosis with a primary or a metastatic tumour is possible because the tumour presents mainly as a complex mass that may contain areas of increased echogenicity [8].

Other signs of infection, as peripheral chorioretinitis or cataract, cannot be diagnosed by ultrasound [9].

**TOXOPLASMA**

When acute infection with *Toxoplasma gondii* occurs during pregnancy, the parasite can cross the placenta and infect the foetus. The ultrasound diagnosis of foetal abnormalities (especially cerebral involvement) usually indicates a poor prognosis.

Abnormalities in 22-45% of infected foetuses are usually revealed by ultrasonographic examination [10, 11]. The abnormalities were unilateral or bilateral dilatation of the ventricles, hydrocephaly, ascites, hepatomegaly or hepatosplenomegaly, intrahepatic calcifications, intracranial calcifications, bilateral hydronephrosis [9], temporary intrauterine growth retardation (IUGR) at 27 weeks with spontaneous catch-up growth.

**RUBELLA**

The classical congenital rubella syndrome [12] comprises cataracts, deafness and congenital heart disease. Congenital infection occurs due to transplacental transmission of the rubella virus, and involves 50% of embryos in the first month of life, progressively decreasing the incidence up to 25% in the second and 10% in the third trimester [13].

The ultrasonographic technique in the evaluation of congenital rubella syndrome has limited value, as cataracts is unvisualizable. Heart defects are present in 20-35% of foetuses, almost all infected during the heart organogenesis period (first eight weeks of life). The most common heart defects are patent ductus arteriosus and peripheral pulmonary stenosis [13], but are also reported interventricular and interatrial septal defects [14].

**CYTOMEGALOVIRUS**

Cytomegalovirus (CMV) represents the most common foetal infection, as affects 0.2-2% of foetuses [15], is considered a major cause of serious neurological sequela in newborn infants. There is a direct relationship between time of infection and severity of lesions. Transplacental transmission is the main street for perinatal infection; it can occur both during a primary or a reactivation of a maternal infection. The rate of transmission is about 40% in primary infections and about 1% in reactivations [16]; the reactivation infections account for 30% of congenital infections [17] but virtually never cause severe congenital disease [16]. About 15% of infected foetuses will have clinical apparent disease with 90% long term sequelae, and 15% of asymptomatic
infected infants will develop long term sequelae [13].

The most common ultrasound findings include IUGR, microcephaly and cerebral and intrahepatic calcifications. The ultrasonographic abnormalities are generally associated with more severe disease [18] but often in the infected fetus the ultrasound scan is normal [13].

IUGR is often the first sign of foetal CMV infection: it is generally an early onset symmetric IUGR, with frequently disproportion between head biometry and limbs, due to microcephaly.

Fetal Central Nervous System (CNS) CMV involvement includes hydrocephalus, ventriculomegaly (as dilatation of posterior horns of lateral ventricles), echogenic vessels in the basal ganglia, and microcephaly and periventricular calcifications.

Recently has been shown that a transvaginal scan may detect signs of cerebral CMV vasculitis in a 30 weeks gestation foetus, as bilateral ventriculomegaly, thin synchiae dividing the occipital horn into two compartments, subependymal cysts and punctate hyperechogenic foci observed in the periventricular region [20].

Single or multiple hepatic intraparenchimal calcifications, ascites and hydrops [18, 21], hyperechogenic foetal bowel [22] probably due to bleeding resulting from thrombocytopenia induced by an overwhelming systemic CMV infection, and oligohydramnios [18] are other ultrasonographic signs. It has to be taken into account the natural history of the foetal infection due to CMV and other agents in the evaluation of a single foetal ultrasound abnormality.

Stein et al. [2] reported a foetus with a single intrahepatic calcification with no other findings at 21 weeks, and multiple intrahepatic calcifications and microcephaly at 33 weeks, with severe neurologic dysfunction and death at 3 months of life.

Peters et al. [22] reported a diagnosis of hyperechogenic foetal bowel at 18 weeks; further ultrasound scans revealed progressive lateral ventriculomegaly, IUGR and foetal hydrops, with intrauterine death at 33 weeks.

On the other hand, Weiner and Grose [23] described a case of CMV infection with pericardial effusion at 23 weeks, which resolved in 1 week: the infant had no signs of congenital infection.

HERPES SIMPLEX

Intrauterine infection due to Herpes simplex virus (HSV) type II has been associated with a significant number of neonates HSV infected. The association of this disease with elevated alfa-fetoprotein, positive amniotic fluid acetylcholynesterase and ultrasonographic abnormalities has been described by Lanouette et al. [24]. These Authors describe a 28-year-old nullipara at 19 weeks gestation with an abnormal triple test; possible ventriculomegaly, hyperechogenic bowel, persistent flexion of the legs are revealed by an ultrasound scan. Repeating scans revealed hepatosplenomegaly, an hyperechogenic intrahepatic mass of 1.1 cm (afterwards revealed as a subcapsular calcification), and an increased echogenicity in the peritalamic region and in the cerebellum, solid echogenic debris attached to the foetus in the flank regions, the sacrococcygeal area and the fingers.

VARICELLA

Varicella in pregnancy has approximately an incidence of 7/10,000 pregnancies [25]. The risk of foetal involvement seems to be linked with gestational age at the time of maternal infection: the term of 20 weeks of pregnancy seems to be the turning point between the risk of congenital varicella syndrome (risk <4%) and that of zooster for the infant (risk <2%) [25].

According to Alkalay [26], the description for congenital varicella syndrome, includes IUGR (39%), cutaneous lesions on a dermatome (100%), neurological abnormalities (77%), microcephaly (12%), ocular anomalies (68%), skeletal anomalies (68%) especially homolateral hypoplasia of members, cutaneous lesions and hypoplasia of fingers, gastrointestinal lesions (23%) with stenosis or atresia and genito-urinary anomalies (23%).

From an ultrasonographic point of view the lesions due to varicella infection are polyhydramnios (75% of infected foetuses) or oligohydramnios, IUGR, foetal hydrops, ascites, hyperechogenic images of the liver with or without hepatomegaly, hyperechogenic lesions in the foetal lungs and myocardium, a limb abnormally shortened, limbs bent or a malposition of the hands, a hydrocephaly or a microcephaly, a neurological bladder, rarely a microphthalmus [27-29]. The viral effects on the foetal CNS could be the main pathogenic process leading to a variety of characteristic anomalies, as duodenal stenosis, dilated jejenum and small left colon. Denervation of limbs could lead to decrease in muscle mass and bone growth with secondary limb hypoplasia, equinovarus and calcaneovalgus [26].

Due to the rare occurrence of varicella in pregnancy and the low risk of foetal varicella syndrome, limited to the first 20 weeks of pregnancy, the ultrasonographic supervision of pregnancy has a central role in the management of these pregnancies.
PARVOVIRUS B19

Parvovirus B19 is a DNA virus of high infectivity, that cause a 20-50% of risk of infection in case of contact with a non-immune individual (about 50% of adult population). The transplacental passage rate is 33% [30]. The true risk of foetal infection would be 5-16% [30]. There is no clear evidence that parvovirus B19 is teratogenic. The most common presentation of B19 foetal infection is foetal hydrops with or without severe anaemia, congestive heart failure with generalised fluid retention [13]. The rate of foetal death following B19 infection is about 9% [30].

OUR EXPERIENCE

In case of suspect foetal infection, our group follows the diagnostic scheme reported in figure 1. Regarding the ultrasound scan, we perform a transvaginal approach, in addition to the transabdominal one in case of cephalic presentation, to better evaluate the intracranial anatomy.

Our ultrasound diagnostic scheme is the following:
— intracranial anatomy: besides the standard biometric evaluations (biparietal and fronto-occipital diameter, cranial circumference, measurement of cerebral ventricles) we carefully search for the presence of calcifications, in particular in the choroid plexa and along the mean cerebral artery;
— splancnic anatomy: we carefully evaluate the hepatic and splenic biometry, the bowel echogenicity and the presence of intraabdominal calcifications. In particular, we measure foetal spleen with foetal abdominal scan crossing the stomach and umbilical vein bend. The anteroposterior diameter is measured positioning the calipers on the splenic part nearby spina and anterior abdominal wall. The longitudinal diameter is perpendicular to the anteroposterior. Fetal liver is measured with a sagittal scan of foetal trunk, measuring the distance between the right hemidiaphragm and the distal part of right lobe;
— hydrops: accurate research of pleural, peritoneal and pericardial effusions;
— evaluation of foetal growth. In particular, we perform serial measures of biparietal diameter, abdominal circumference and femur length. The foetal weight estimate is performed by the Hadlock formula [31];
— placenta: evaluation of morphological characteristics and thickness of placenta;
— amniotic fluid: evaluation of amount.

We perform an ultrasonographic follow up, regarding on gestational age and foeto-maternal immunological status, every 1-4 weeks with a complete morphologic examination and a careful evaluation of foetal growth.

CONCLUSIONS

The recent progresses in the diagnosis of foeto-maternal infectious diseases are principally due to the availability of high resolution ultrasound transducers, allowing us a better evaluation of foetal anatomy, and a correct visualisation of umbilical cord, with a consequent relatively safe sampling of foetal blood.

The principles of managing transplacental infection are to confirm maternal exposure and to assess chance and severity of foetal involvement. In these diagnostic steps ultrasonography plays a crucial role, as non invasive and replicable technique to evaluate the foetal anatomy and to assess the entity of foetal damages.

REFERENCES

ULTRASONOGRAPHIC INVESTIGATION IN MATERO-FOETAL INFECTIOUS DISEASES

SUMMARY

Introduction. Central issues in Perinatal Medicine, for their impact on the mother and fetal well-being actually are infections and immunology. New diagnostic tools in immunological and ultrasonographic techniques allow us to evidence in utero several infectious diseases. Ultrasonographic signs of foetal infections. The foetal responses to infections are dependent both on the infectious agent and the gestational age. The TORCH acronym indicates the affinities among different infectious diseases. Several ultrasonographic signs (IUGR, ventriculomegaly, intracranial calcifications, microcephaly, intrahepatic calcifications) similar in different pathological situations are described. Infectious diseases of the foetus. The clinical and ultrasonographic findings of the most common foetal infectious diseases (Toxoplasmosis, Rubella, CMV, Herpes simplex, Varicella, Parvovirus B19) are described. Ultrasonographic approach. Our ultrasonographic diagnostic protocol is presented, with evidence to the different ultrasonographic approaches in various foetal districts. Conclusions. Ultrasonography plays a crucial role in the assessment of chance and severity of foetal involvement in case of transplacental infectious diseases, as accurate evaluation of fetal anatomy and essential complement of invasive diagnostic and therapeutic procedures.

Key-words: Ultrasound. Infectious diseases. Foetal infection.