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Infective diseases during pregnancy and their teratogenic effects

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Summary. - TORCH group infections (toxoplasmosis, others, rubella, cytomegalovirus, herpes) are the most serious infectious diseases during pregnancy due to the seriousness of possible embryo-fetal lesions. Rates of trasmission and degree of the damage on the product of conception have been described as well as congenital malformation pictures and neonatal illness still observed following to Toxoplasma, HSV, VZV, CMV and Rubella virus infections. Too often, it is very hard to discriminate between primary and recurrent infections in pregnancy, notwithstanding the possible implications. Since at present, neither effective vaccines nor resolutive therapies are available against viral infections, the main means against infection of the foetus still remains the prevention of infections in the pregnant woman.

Key words: infections in pregnancy, teratogenic infections, congenital anomalies.

Riassunto *(Le malattie infettive in gravidanza ed il loro effetto teratogeno).* - Le infezioni del complesso TORCH (toxoplasmosis, others, rubella, cytomegalovirus, herpes) sono responsabili di malattie infettive molto pericolose se contratte durante la gravidanza a causa della loro possibilità di determinare danni al prodotto del concepimento. Gli autori hanno esaminato il rischio di trasmissione dell'infezione e l'entità del danno al prodotto del concepimento in relazione all'epoca di gestazione. Sono state descritte le malformazioni congenite che ancora si osservano conseguentemente all'embriopatia da Toxo, HSV, VZV, CMV e Rosolia e i polimorfi quadri clinici dei neonati infettati. Poiché, ancora allo stato attuale, per tutte le infezioni virali non sono disponibili vaccinazioni sicure né terapie adeguate nei confronti delle malattie e per la difficoltà diagnostica a discriminare un'infezione primaria da una ricorrente, la battaglia contro le infezioni del prodotto del concepimento deve essere basata essenzialmente sulla prevenzione dell'infezione materna.

Parole chiave: infezioni in gravidanza, infezioni teratogene, infezioni congenite.

Introduction

The relations among infective diseases and pregnancy should be investigated from different points of view. Some infective diseases are consequence of the pregnancy, such as endometritis, puerperal infections. In others, the extend and the deed of some infections may be modified by ongoing pregnancy.

It is well known, for instance, that a pregnant woman is particularly sensitive to infections of the urinary organs. Infective disease may also influence the course of pregnancy.

A further aspect of the topic lies in the possibility for an infective disease to sway the normal course of pregnancy. This may happen either in direct or indirect and non specific way, causing breathing disorders, hear and circulatory problems, convulsion and hydroelectrolytical unbalances which may have negative impact on the fetus.

Vertical transmission infection constitute a further standpoint of the complex relation between infective diseases and pregnancy. These may induce abortion, intrauterine death, prematurity and congenital infections. The vertical transmission of an infection may take place in different manners: either the pathogenic agent diffuses through the placenta or an ascendent infection of the woman's genital duct occurs. The latter is usually upheld either by various agents responsible for venereal diseases or by common vaginal saprophytes. This type of transmission is usually more frequent towards the end of the pregnancy, mainly after the membranes have broken. Furthermore, infection of the fetus may occur during delivery.

Luckily, clinically relevant prenatal infections are rather infrequent events (infective diseases are accountable for congenital malformation only in 1-2% of the occurrences). This is due to existence of complex means of protection. The placenta is a powerful barrier with a wide variety of macrophagic cells. It allows transit of maternal IgG while inhibits a large number of infective agents from reaching either the embryo or the fetus.

Furthermore, between the third and the fifth month, the defensive systems of the fetus, first the humoral then the cellular one, begin their development. There are numerous infective agents commonly known to be cause of pathological conditions for the embryo and/or the fetus. Among these, some have rather modest relevance from an epidemical point of view, at least in Italy. Others are of greater importance because of the frequency and the seriousness of the infections in the fetus and/or the embryo. Particulary, this applies for the agents of the TORCH complex.

Toxoplasmosis

Toxoplasmosis is an usually benign anthropozoonosis, however, it may become a very serious disease if contracted by a pregnant woman or an immunodepressed individual.

Such an infection is widespread even though it exhibits large oscillations. Studies carried out on pregnant women had shown antibodies prevalence which varies from 12.5% in Oslo, to 32% in New York up to 84% in Paris [1-3]. Prevalence increases with age and is correlated with eating habits, hygenic conditions and cohabitation with the cat.

In our country, the antibodies prevalence has been observed to vary from 32.2% to 79.6%, being remarkably higher in rural areas [4-6]. These data enable one to infer that 16-87.5% of pregnant women may possibly contract the infection with a risk of seroconversion estimated about 0.15-0.6% [2].

In order to assess the change of transmission to the embryo and/or the fetus, one should establish when the maternal infection took place. Indeed, if the woman was infected before conceiving there is no risk of transmitting the pathogenic agent to the fetus. Studies carried out in various countries, let estimate the risk of congenital toxoplasmosis as ranging from 0.5 to 6.5 occurrence for 1000 born alive babies [1-3, 7, 8].

It has also been observed that the contigency of transmitting the disease increases during the pregnancy, going from 20-25% in the first three months to 35-54% during in the last three months [1, 9-11]. On the contrary, the seriousness of the clinical displays decreases as long the pregnancy proceeds.

Abortion, perinatal death and congenital infections occur only if the mother contracted the infection early in the pregnancy.

In 41-54% of cases, babies infected from the fourth month of pregnancy onwards do not show any clear clinical symptom [1, 9-11]. Congenital toxoplasmosis has various clinical symptoms, sometimes they are not specific of the disease and resemble the symptoms of other congenital infections. Only 10-15% of the infected babies show at birth, in various proportion, clear symptoms such as skull and encephalic anomalies, neurological afflictions, intracranial calcifications and eyes anomalies. Moreover, only 5% of them exhibit severe clinical evidences such as an acute generalized form of illness (thrombocytopenia, anemia, jaundice, hepatomegalia, maculopapular rash, CNS sequelae). The classic triad hydrocephalus, chorioretinitis, and intracranial calcifications is in reality very rare. When these instances take place 1-6% of babies die in a short time [1, 2, 9, 10].

Those babies who do not show specific symptoms should be carefully observed, as they may develop ailments such as chorioretinitis or neurological symptoms even, in 80-90% of cases, several years after their birth [1, 9, 10].

In order to prevent such an infection and to reduce the effects on the fetus, it is very important to know the serological status of the expectant mother. Since correct screening before pregnancy lacks, such an investigation is very often carried out only between the third and the sixth month of pregnancy. In case of positive outcome, these late testings do not allow to trace back possible contagion and to formulate correct diagnosis.

The infection of the mother is certain when documented seroconversion is present, in any other case, the diagnosis is based on the behaviour during time of the antibodies (fourfold or larger increases of antibodies title or positive class IgM antibodies are diagnostic clues). Presently, thanks to specific diagnostic tests such as DS, IgM-ELISA, IgM ISAGA, Anti P30 IgM, it is possible to identify with greater certainty the moment when the infection took place [1, 6-8, 10, 13]. It is always important to begin the specific treatment, because, although the risk is not reduced, the likelihood of fetal infection may be reduced by as much as 60% [1, 10]. The availability of sensitive and reliable techniques for prenatal diagnostic enables one to verify whether fetal infection occurred. The diagnosis can be confirmed by demonstrating persisting or rising levels of specific IgG antibodies, presence of IgM antibodies in cord or neonatal sera, and isolation of *T. gondii* from placenta or cord blood and the segregation of the protozoon through injection in a rat. It is appropiate to undertake a correct diagnostic action also for those babies who exibit congenital infections. Such an action would reduce the impact of long term consequences [9, 12, 13].

In addition to periodical serological tests, it is also necessary that, in order to reduce the risk of contagion, seronegative women adopt generic and specific hygienic measures such as to wash the hands, to avoid contact with pets and animals, and to observe particular alimentary habits.

Rubella

Despite the well known danger of the rubeolic infection, when contracted for the first time during pregnancy, 12-24% of women became pregnant without being immune to such a disease. For these women the possibility of seroconversion is 1-2% with likelihood of transmitting the infection to the fetus at any time during the gestation [14, 19, 22]. In unusual cases, it has also been observed the reinfection of women who either had previously contracted the disease or had been vaccinated. In such case the risk of transmission to the fetus is very low, less than 5% for scarce or lacking viremia [15, 16]. The onset of the rubeolic infection inside the uterus and the appearance of the infection in the fetus depend from the time in the pregnancy in which the mother had rubella. The eventuality of transmission of the disease to

the fetus has been evaluated at 80% during the first 12 weeks of gestation, 55% within the 16th week, 36% within the 22nd week, 30% within the 30th week and 100% if the mother exibits rubella in the last month of pregnancy [17]. The subjects infected at birth show clinical polymorphic displays of congenital rubeolic SD which relate to the virulence of the viral groups and, above all, to the period when the infection took place. If the mother contracted the infection during within the 12th week of pregnancy, 50% of newborn bear ear malformations with deafness, malformations of the cardiovascular systems and malformations of the eye which almost invariably involve retinitis pigmentosa, cataract and rarely microphthalmia and glaucoma. The fraction of neonates born with malformations reduce to 35% and 10% if the mother was infected at the fourth or fifth month of pregnancy respectively [18, 19].

Among the babies born from mother infected by rubella more than 50% are normal at birth, but, in following years, develop one or more symptoms of disease (Expanded RS). These are, in decreasing frequency order: loss of hearing (which may appear as the only deficit), mental deficiency, mycrocephaly, progressive panencephalitis. In addition to these damages, usually permanent, one may also find haemolytic anaemia, hepatosplenomegaly, growth retardation for a deficit of GH, thrombocytopenic purpura, kidney defects, dental malformations, bone defects, and seldom pneumonitis and encephalitis [19, 20]. Within the CRS one may ascertain late manifestations (sometimes even several years after birth) likely due to the persistence of the virus with subsequent damages to the immune systems. These manifestations include, in decreasing order of frequency: diabetes mellitus, glaucoma, progressive panencephalitis, thyroid pathologies, keratoconus and corneal hydrops [18, 21, 22].

The diagnosis of CRS should be presumed when there is a positive maternal anamnesis for rubella proven or not by serological means and/or the baby exhibits clinical displays consistent with ailment.
Incontrovertible diagnosis can be carried out by:

1) isolation of the virus in nasopharingeal secretion, LCS, as the newborn eliminates the virus after the first year;

2) revealing the presence of specific IgM persisting from the sixth to the twelfth month (HAI, Nt test);

3) observing the persistence of anti-rubella IgG, particularly if with high title between the sixth month and the fourth year of age [19, 22]. In any case it is necessary to keep the newborns under control in order to identify both already stable damages and those which may became noticeable during subsequent years. These do not have therapy other than the syntomatic and support ones.

Prevention of CRS is subject to the immunitary protection of fertile women who did not contract the disease in childhood.

Presently, for this purpose it is used the Wistar RA 27/3 viral strain, attenuated and cultivated on human diploid cells.

Clinical diagnosis of pregnant woman risking rubella is not reliable. The primary infection, usually clinically manifest, may also have a subclinical course or be mistaken with an enterovirus infection such as HPV-B19, CMV, MNI. Therefore, it is fundamental to carry out the serological analysis employing various tests such as ELISA, RIA, HAI which are able to pinpoint specific IgG and IgM. When the infection occurs, it is symptom of recent infection the increase of specific high title IgM in two consecutive takings (IgM remaining positive for one month at least). The observation of specific IgM, even low title, in the late stage of the disease, with concomitant increase of IgG title, is a sign of recent primary infection [23]. To differentiate between primary infection and reinfection is useful in order to decide the correct clinical treatment of the patient. Primary infections display simultaneus increase of specific IgG and IgM, whereas reinfections are characterized by the increase of IgG only, being any increase of the IgM of lesser extent or absent.

In recent years, the two forms of infection have been more efficiently differentiated thanks to an avidity test for the specific IgG. In the primary infection the IgG avidity develops slowly, whereas in the reinfection it appears higher from beginning [24, 25].

Presently, the are no satisfactorily techniques to diagnose prenatal infection, since the search of IgM in the blood of the fetus can be carried out only at later stage (following the 23rd week). This is true also if the mother infected only recently. However, techniques are being refined which should inprove the possibility of prenatal diagnosis. Such techniques employ RNA probe and PCR to search for the virus in the amniotic liquid or in the chorionic villi [26].

Cytomegalovirus (CMV)

CMV is a herpes which has general diffusion. Normally it causes asymptomatic infections in immunocompetent subjects, even though such an infection may emerge as mononucleosis-like infective disease. This is the infection most commonly transmitted to the embrio and/or the baby. The rate, worldwide, range from 0.2 to 2.3% of all babies born alive [27]. The highest risk of infection of the fetus through the placenta associates with primary infection of the mother (20-30%). However, it has been documented, albeit at a lower level (0.5-2%), the association due to reinfection or reactivation of the latent virus [28]. Specific CMV antibodies present in the mother do not impede the transmission of the virus through the placenta. However, such antibodies may perform a protective action as proven by less serious effects on the fetus [29].

Fertile seropositive women range from 57 to 92% and, among these, 14% relieve themselves from the virus with the secretion of the cervix [30]. If the excretion of CMV takes place during delivery, the risk of the infection being transmitted to the newborn increases because of the possible perinatal transmission. An ascending path of the infection is possible, albeit unlikely.

The risk of seroconversion in pregnant receptive women has been evaluated to be about 0.6-4.1%. Such a risk is comparable to the risk faced by not pregnant women. Transmission of the infection to the fetus is possible at any time during the pregnancy, although it is less likely in the first six months (20% 1-3 months, negligible 4-6 months) than in the last three (50%) [22]. Despite the infection being less likely early in the pregnancy, the risk of congenital anomalies, mainly in the CNS, is higher [27]. There is a direct correlation between duration of the infection in the uterus and the seriousness of the ailment afflicting the newborn. 90-95% of the babies born infected do not exhibit specific symptoms, but, among them, 5-10% show intellectual and auditory deficits within the first two years of life [31]. 5-10% show at birth clinical manifestations such as mycrocephaly, intracranial calcifications, hepatosplenomegaly, pneumopathy, anemia, thrombocytopenic purpura, chorioretinitis and low weight.

When the disease does no induce death, it gives rise, on the longer term, to permanent outcomes like mental deficiency, auditory deficiencies as serious as total deafness, sight deficits and dental defects [32]. Babies born whith congenital CMV are usually delivered by mothers affected by primary CMV infection. Very rarely reinfection or recurrent infection lead to symptomatic disease. Whenever this happens, the disease shows less severe consequences and the long term effects are almost totally absent (0.1%) [33]. Also the perinatal infection may give rise to symptomatic infection of the fetus showing at birth limited clinical evidences such as hepatosplenomegalia, lymphadenopathy and anaemia. These symptoms have, in the longer term, bening outcomes.

The diagnosis of the viral infection is carried out both by isolating, within the first two weeks of life, the virus in urine, saliva and tear drops of the newborns or by the presence or late emergence of specific IgM [23].

Laboratory techniques are very important also in order to diagnose the acute infection of the mother. This is revealed by isolating the virus in bodily fluids (urine, saliva, secretion of vagina and cervix) via coltural or by electronic means (electronic microscope). The only detection of the virus does not enable one to discern between primary infection and reinfection. Even serology with tests able to detect (anti-cytomegalovirus IgG, IgM) antibodies (FC, IF, RIA, ELISA being the latter the most commonly used) provides information frequently inadequate to discern between primary infection and reinfection. A fourfold or higher rise in the title of IgG denotes recent infection, however such fluctuations may occur also in healthy seropositive women [34]. Proof of seroconversion indicates primary infection, therefore serological screening before conception is extremely important in order to differentiate, during pregnancy, between primary and recurrent infection. Whenever there is the possibility of primary infection of the mother and therefore of an infected child being born, it is appropriate to carry out amniocentesis and/or cordocentesis. These analyses confirm whether the fetus is infected and allow one to take appropriate actions.

Varicella-Zoster virus (VZV)

VZV infection, which causes a benign illness in childhood, can cause severe and possibly deadly lung affections in pregnant women. The infection is transmitted to the fetus and the consequences for the newborn depend from the moment during pregnancy when contagion developed [35]. Since it is an extremely common ailment of childhood, the great majority (80-95%) of fertile women is immune to the disease. This yields low rate of acute infection during pregnancy (0.1-0.7 per thousand) [36]. During the first three months of pregnancy, the disease associates with infection of the fetus which causes congenital anomalies in the neonate [37-39]. It is difficult to evaluated the rate of such anomalies (0.9-1%) even though it may reach 10% [40, 41]. The disease, if contracted in the last six month of pregnancy, is not associated with malformations. An exception is given by only case reported in literature of a newborn who exhibited cutaneous ulcers due to chickenpox contracted by the mother at the 28th week of pregnancy [42].

The malformation syndrome features respectively and in decreasing order: cutaneous, neurologic, musculoskeletal and ocular lesions. It also includes delays to the intrauterine growth and neonatal herpes zoster. One of four newborns will become infected when maternal varicella occurs during the last 3 weeks of pregnancy.

The seriousness of the infection is strictly tied to the time when the exanthema of the mother appeared [43]. If this would appear from 21 to 5 days before delivery also the newborn will exhibit the lesions within the first four days of life. The disease will be of moderate extent and with benign course. When the maternal exanthema appears in the last five days of pregnancy or in the two days following delivery, the disease of the baby can manifest between the fifth and the tenth day of life. The illness may be mild with only a few cutaneous lesions, or may become severe with fever, hemorrhagic rash, and visceral lesions. The mortality rate is about 30% and death usually is due to severe pulmonary and brain diseases.

Herpes zoster during pregnancy has been observed only very rarely (0.5 cases in 100,000 pregnancies) and does not seem to be associated with an high rate of congenitals anomalies, albeit a small number of newborn having mother affected by zoster have shown malformations such as microcephaly, microphthalmia, cataracts, and talipes equinovarus [22,44]. When dealing with neonatal infection, early diagnosis is crucial for those newborn having mother affected by chickenpox from 5 days before to 3 days after delivery. They should be treated with specific immunoglobulin (VZIG 125 U) in order to reduce the gravity of the disease [45]. Usually the diagnosis is clinical, but laboratory techniques confirm it by using fast methods on samples obtained by vesicular lesions of the mother. These methods are: identification of virus-specific antigens by IF and MoAB, the search of the virus with the electronic microscope in negatively colored samples of vescicular lesions. When there is uncertain response, the virus can be isolated from vesicular fluid by inoculating freshly collected specimens onto human diploid cell lines [23]. Serological tests may also be used to confirm the diagnosis of chickenpox. These are either proof of seroconversion in serums procured within an interval of 10-15 days or the, at least, fourfold increase of specific IgG with methods including FC, IF, Nt, FAMA, ELISA. The latter method is gaining widespread diffusion to identify the VZV antibodies [46]. The observation of IgM is always a sign of recent infection. IgM is observed only one thirds of the cases in eligible women. For the remaining two thirds, the diagnosis of active primary infection is carried out only when a fourfold or larger increase in the specific IgG is observed.

Herpes simplex virus (HSV)

The herpes simplex virus, along with the two serotypes HSV1 and HSV2, exhibits a range of clinically similar displays. However, HSV1 causes mainly gingivo-stomatitis, pharyngitis and is responsible for genital infection only in 7-50% of the cases, whereas HSV2 is primarily involved in genital herpes (85% of primary infections, 99% of recurrent forms) and in neonatal herpes [47].

The risk that such a virus may be transmitted to the and/or the fetus is estimated to be about 40-50% when the mother contracts primary infection during the pregnancy. If the mother contracts the recurrent infection, which is the most common during pregnancy, the risk is about 5% [48, 49].

Viral contagion occurs during delivery and only rarely takes place via transmission through the placenta. The latter type of transmission is associated with the primary infection spread by the mother during the first three months of the pregnancy and causes serious consequences for the development of the fetus [50]. These may involve an increase in the likelihood of abortion (25%), of death at birth and of congenital malformations in area such as the skin, the central nervous system (CNS), the eyes or the liver [36, 51].

Infection given to the fetus inside the uterus was observed also following primary infection of the mother in the last three months of gestation. However, only rarely infections befalls as a consequence of recurrent disease during the same months. Moreover, the great majority of discovered intrauterine infections were caused by HSV2. These are rather rare occurences as the yearly rate of primary infection during pregnancy is about 0.58% [52].

The most common mean of transmission of the virus to newborn is contagion during delivery while inside the birth duct. When the mother is affected by primary infection, the newborn has 50% likelihood to be infected. In such cases the neonatal infection is always symptomatic and very serious [48]. In the newborn the infection may be either localized or generalized. 20% of all the occurrences of neonatal herpes show localized manifestations in the skin, in the eyes, in the oral cavity. These become manifest by 10-12 days after birth. Cutaneous and mucosal lesions may range from simple bullous to pustular lesions, whereas eyes lesions are chorioretinitis and keratoconjunctivitis. 25% of these babies will exhibit, at later time, neurological anomalies, even though during the neonatal period CNS does not appear to be involved. 20-30% of neonates, however, show localized involvement of CNS with or without lesions of the skin. These become manifest 15-17 days after birth. The diagnosis is serious, as 17% of the cases treated with anti-viral and 50% of those not treated die. Moreover, 40% of the survivors will exhibit neurological followup such as psycomotor retardation.

Not less than 50% of newborns with neonatal herpes have a generalized infection which involves several organs such as liver, spleen, kidneys, suprarenal glands, digestive system, pancreas, heart and, in 2/3 of the cases, also CNS. The death rate of such a form is 80% and reduces to 20% if the disease is adequately treated with antiviral drugs. 20% of the forms generic or localized to the CNS exhibit neither typical nor atypical lesions of the skin, therefore the neonatal diagnosis of the affection may be difficult [22, 32]. The diagnosis of this infection is carried out by isolating the virus from bodily secretions such as urine, saliva, nasopharyngeal secretion, vescicles fluid [53]. The diagnosis can also be performed either looking for intranuclear inclusions in the cells of the vescicles' fluid, or by checking for the antigen viral in samples of the tissues using specific monoclonal antibodies. Serology does not provide any help in the diagnosis of the newborn.

The strategy of trying to prevent perinatal transmission by identifying mothers likely to be infectious at the time of delivery and them performing cesarian sections in these cases has been fraught with difficulties.

Hepatitis B virus (HBV)

The hepatitis B virus is widely diffused in the world and, within broad local geographical variations, it has been calculated that 350 millions people are chronically infected HBV carriers. These are at high risk of death from chronic liver disease and primary liver cancer, diseases which kill over one million people per year. These carriers are mainly responsible for the spread of the infection as they are often asymptomatic and unaware of their potentially infective status.

Vertical transmission of HBV is prevalent in countries with high endemic status such as those of South-East Asia. There, it has been observed a 40% presence of HBsAg in pregnant women. In our country, the presence of HBsAg exhibits wide geographical variance. It is about 1% in the North, whereas it reaches 5% in some areas of Southern Italy. It is always lower than in countries with high endemic status [54, 55].

The transmission of HBV to the fetus may take place during pregnancy (intrauterine infection) or during the delivery (perinatal transmission). The possibility of intrauterine infection has been proven by autopsies carried on fetuses aborted by HBsAg positive mothers [56]. This type of contagion is thought to be accountable only for 5-10% of vertical transmissions of the disease [57]. This type of contagion is presumed when HBsAg is found in the blood of the newborn within the first month of life. The discovery of such an antigen in the umbilical cord is however debatable, as some authors argue it is possibly due to the labour of delivery, rather than to infection of the fetus [58, 59].

To reveal specific IgM antibodies in the newborn's blood or in the umbilical cord is not, contrarily to other infections, of any help. Anti-HBc IgM types have never been found in any occurrence under these conditions [59, 60].

There are still uncertainties regarding the way the intrauterine infection takes place. Some authors suggested the virus' transmission during pregnancy through the placenta, while others correlated the intrauterine infection with the presence of HBsAg in the amniotic liquid (found to be 26-33% in HBsAg+ pregnant women) [58, 61].

Within the vertical transmission, the perinatal infection is prevailing. This type of infection is, in high endemic countries, one of the primary sources for the diffusion of the virus.

The serological status of the mother has a definite influence on the likelihood of transmission. HBeAg positive pregnant women, which are affected by HBV infection, with high viral replication, transmit the infection to the fetus in 60-100% of cases. On the contrary, if the pregnant women is a chronic carrier of anti-HBe, with low viral replication, the likelihood of HBV transmission decreases to 5-12% [54, 55, 62-66].

There are some eventualities regarding the way the perinatal infection takes place. It has been proven that during the labour of delivery is possible a transfusion of maternal blood to the fetus. This appear to be accountable for 50% of the infections, wich are shown by the presence of HBsAg and/or HBV-DNA in the cord blood. On the other hand, 93% of the samples of vaginal fluid of HBV carriers contained HBsAg, therefore also the passage through the birth duct may expose the baby to infection. Furthermore, in 93.5% of cases such an antigen was found at birth in the gastric secretion of the newborn [61]. One may therefore presume infection due to ingestion, possibly with passage of the virus through the mucosas of the mouth rather than through the enteric via. The latter is not known, at least in older age, to be a path for the infection [57, 67].

The preeminence of the perinatal infection is also substantiated by the different risk of infantile infection, which depends on the time during pregnancy when the mother manifests acute B hepatitis. Such a risk is nil during the 1st trimester, grows to 6% in the 2nd trimester and reaches 67% in the last trimester.

It becomes 100% if the disease evidences within six week from delivery. The clinical characteristics of the acute disease are, for the pregnant woman, similar to those of patients of the same age.

Vertical transmission to the newborn can be shown by the appearance (95% of the cases), within the first four months, of HBsAg in its blood. On the contrary, one may infer the absence of vertical transmission when the antigen has not been found within the ninth month [68-70]. The infected child may develop clinically manifest disease, possibly severe neonatal giant cell acute hepatitis, but much more often becomes chronic carrier of the virus risking to develop chronic hepatitis and subsequently cirrhosis (25%).

It is essential to prevent the transmission from mother to fetus as this is the only way avert chronic disease in the newborns. In this way, the spreading of the virus among general population is also hindered.

The strategy adopted in our country requires mandatory checks of the serological status of the pregnant women during the last trimester of pregnancy. Whenever the woman would result HBsAg+, the newborn will be subject at birth to preventive treatments (passive and active prophylaxis).

Human immunodeficiency virus (HIV)

From an epidemiological point of view, it would be usefull to consider the problem of perinatally acquired HIV infection in the context of the whole epidemic, as each of these infections is the result of an earlier HIV infection in a woman. AIDS cases in women amount for

9% of total cases in USA, 13% in Europe and 19% in Italy. In all the countries, the most frequent route of transmission is still the parenteral one linked to the sharing of needles during parenteral use of illicit drugs. However, sexual relationship with HIV infected men, in the last years, has become one of the most important route of transmission of HIV infection in women, accounting for 26-31% of all cases in USA and Europe [71]. Adult cases of AIDS due to heterosexual contact diagnosed in USA nel 1989 represent a 36% increase over cases diagnosed in 1988; this increase result higher than for any other transmission category with the only exception of perinatally acquired cases which increase with the same speed (36%). This epidemiological profile could also be found in some European Countries including Italy: according to our experience, as time passes, HIV infection in women and their children acquires even more the characteristics of a real venereal epidemy and so, although still partially, differenciated from drug addiction phenomenon.

The problem of pre- and peri-natal rate of transmission is complicated by several factors:

- difficulty in obtaining cohorts of a significant size;
- choise of correct denominators [72];
- difficulty in a univoc and universal interpretation of results from some diagnostic procedures;
- but mainly the absence of serological and virological testing for the early diagnosis of infection. For example, children who die in their first year of life cannot easily be counted as infected or uninfected unless they have a clinical and immunologic picture characteristic of AIDS or a positive virus test.

The multi-center studies started in the last years allowed to solve some of the problems deriving from sample size and from the need for longitudinal studies which include only infected pregnant women [73]. Actually, the most important longitudinal studies in Europe and USA, with sufficent follow-up of infants, suggest rates of maternal transmission between 13% and 35% [72, 74-79].

Studies made in African Countries usually report a rate of transmission higher than those in more industrialaized countries probably because [80-82]:

- a greater proportion of mothers with symptomatic HIV infection;
- higher loss of babies to follow-up also because of a perinatal mortality significantly higher;
- major difficulties in laboratory diagnosis of infection;
- breastfeeding;
- a higher incidence of chorionamnionitis [82].

The exact definition of the transmission rate represents one of the primary objective essential for any preventive measure and for counselling before and during pregnancy.

The mechanisms of mother-to-child transmission and the frequency of transmission in utero (stage of pregnancy) compared with that during birth when there is exposure to maternal blood and body fluids, is still to be completely explained. Studies of tissues from 15- and 20-week-old aborted fetus from HIV-infected women showed that HIV could be cultured from these tissues and the maternal-fetal transmission could occur by the second trimester of pregnancy [83, 84]. Maury *et al.* have reported that placental tissue expresses CD4 and can be infected by HIV *in vitro* [85].

The placental tissue used in these experiments came from both first-trimester chorionic villi specimens and term placentas. While the precise route of infection of the fetus during maternal-fetal transmission is presently unknown, the presence of nonlymphocytic CD4+ cells within the placenta suggest that HIVinfected maternal lymphocytes may transmit the virus to placenta cells, which in turn could spread the infection to CD4+ cells in the fetal circulation [85]. However, recently, Ehrnst *et al.* [86] by studing 12 aborted fetuses and 27 children of HIV-infected mothers have not shown a correlation between maternal viraemia and spread of HIV across the placenta and, have also shown the absence of signs of infection of all fetuses seen during the first [72] and second [71] quarter. According to these authors, all these observations, indicate that in most cases transmission occurs close to or at delivery when the exposure to maternal blood or body fluids is significative. It might also be possible that each of these factors play a role in the pre- and peri-natal transmission of HIV. Finally, it has already been shown that the risk of contagion for the child of an HIV-infected woman does not end with gestation and delivery. Post-natal infection, through breast feeding has been documented in some cases [87, 88] however, it has not been found in what measure this affects congenital infection in children born by HIV Ab positive mothers and then breast-fed. The definition of the period of transmission and risks related to the period of pregnancy and/or delivery bears a particular meaning in the role of preventive measure which could be adopted.

Chlamydia trachomatis (CT)

The CT infection, accountable in the woman of disorders such as cervicitis and salpingitis may negatively affect the course of pregnancy and the newborn's health.

Rates of CT infection during pregnancy are greatly varying as they range from 4 to 47%. They depend on factors such as age, social and economical conditions, race, previous infection by other sexually transmitted diseases and young age at the first sexual intercourses [89-92]. Among the factors controlling the CT colonization, age is the most important one. Inverse relation with age has been observed in populations having either low or high rate of infection. Common risk circumstances for the CT infections are black ethnical group and low social and economical level [93]. Also

single women, or married women with several sexual partners bear higher infection risk. Similarly, risk factors are previous exposure to other microorganisms (gonococcus, streptococcus, trichomonas) and the pregnancy. The effects of the chlamydial infection during pregnancy are still under scrutiny, however the literature reports disorders such as preterm premature rupture of membranes with preterm labor, and with amniotic fluid infection [94]. The children of infected women and those of healthy ones also display significant differences. Low weight at birth and premature birth were observed, similarly the rate of perinatal mortality appear to be higher than in the reference group (33% *vs* 3.5%) [95, 96]. Referenced studies report that both recent (IgM anti-CT antibodies positive) and severe CT genital infection, occurring during pregnancy, may be cause of complications. Nevertheless, the actual risk associated with CT is still to be evaluated so that it may be possible to estimate whether other genital microorganisms contribute to the onset of adverse phenomena. Furthermore, it is not known whether transmission of the microorganism through the placenta is possible. It is known, however that infected mothers mainly transmit the contagion while the baby is being delivered (perinatal infection) [97, 98].

About 60-70% of the newborns delivered by mothers with positive cervical isolation of CT exhibit chlamydial infection. The infection is proven by seroconversion of antibody title and by the microorganism being present in various organs (conjunctiva, respiratory systems). About 30% of the infected neonates bear a clinically manifest disease [99]. Most significant pathological displays of the newborn are chlamydial conjunctivitis and interstitial pneumonia. Bronchitis, otitis, and gastroenteritis have been observed as well [94]. About 20-40% of the babies delivered by mothers with genital infection develop conjunctivitis which in half of the cases has asymptomatic course. The newborn, when affected by the symptomatic form of the disease, shows inflammation within 5-12th day of life. The ailment may heal spontaneously, but in some cases, micropannus would develop with subsequent blindness.

Conjunctivitis associates, in 50% of cases, with interstitial pneumonia. The symptoms of intersitial pneumonia are tachypnea and intermittent cough. These symptoms appear gradually between the 4th and the 16th week of life and are not coupled with fever. Occasionally, nasal congestion with scarce rhinorrhea is present. Radiographs of the lungs show areas with interstitial or alveolar infiltrates. Only rarely, the babies have pneumonia so serious that breathing assistance is required. In most cases the pneumonia consummates without long term sequeles.

It is fundamental for the diagnosis to isolate the pathogenic agent in the secretion of the eyes, nasopharingeal or bronchi.

Serology with test such as FC and MC contributes to make specific antibodies visible only with pneumonia. Positive IgM titers correlate with presence of pneumonitis and only rarely are seen in infants with conjinctivitis [100].

Parvovirus B19 (B19)

The B19 infection, responsible in childhood of erythema infectiosum, if crontracted during pregnancy can be transmitted to the fetus and cause its death for hydrops [101]. The present level of knowledge estimates the risk of transmission to the fetus as ranging from 15 to 50%. Up to now, there are no clues of congenital anomalies associated with such an infection. Children born by infected mothers have been found to have only serological traces of intrauterine infection (specific IgM in the fetal blood), without displaying any disease or anomaly at birth [102]. An important aspect of the presence of the virus during pregnancy is the death of the fetus. The risk of fetal death is maximum between the tenth and the twentieth week with abortion rate of 15% within the 12th week and of 17% between the 10th and the 18th week. The risk of fetal death during the pregnancy is lower than 10%. Women who are serologically positive for specific B19 antibodies are disposed to infection. From 47 to 70% of fertile women yield negative specific B19 serological tests [103, 104].

The great majority of the infrequent infections of pregnant women occurs because of contacts with children infected by erythema infectiosum, since this disease is in fact more common during the first two decades of life. Therefore, a negative pregnant women should avoid contacts with infected or presumably infected children, even if the viremia was revealed seven days before or three days after the appearance of the skin rash. When the symptoms appear, the maximum risk of infection had already been taken [105].

If a pregnant women has typical displays of B19 virus infection, such as erythema or arthritis, it is required to search for specific antibodies in samples of maternal serum. The presence of IgM coupled with a clinical display of disease are highly indicative of primary infection, whereas the IgG seroconversion can be caused by either primary infection or repeated exposure to the virus. The serological investigation carried out by means of ELISA and RIA [23]. Highly specific for the diagnosis of acute infection is also to reveal antigens from serum, urine, secretions by IF with monoclonal antibodies or DNA by DNA probes. The specific diagnosis of infection is often incomplete because about 50% of the people infected by Parvovirus B19 show atypical symptoms and up to 25% of the cases are asymptomatic.

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