



Review

Pregnancy outcome following infections by coxsackie, echo, measles, mumps, hepatitis, polio and encephalitis viruses

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Received 30 August 2004; received in revised form 12 December 2005; accepted 23 December 2005

Abstract

Women may be infected during pregnancy with infectious agents that are often passed unnoticed; however, the causative agent may still traverse the placenta and infect the developing embryo and fetus. Several of these agents (i.e. rubella, cytomegalovirus or *Toxoplasma Gondii*) may cause severe fetal damage, but most other infections in pregnancy seem to be much less dangerous to the fetus. In this review we discuss the effects of several viral infections during pregnancy where the effects on the developing embryo and fetus are infrequent, but they may sometimes cause severe neonatal disease. The following viruses are discussed: coxsackie and echoviruses, measles and mumps, polioviruses, Japanese and Venezuelan equine encephalitis viruses, West Nile virus and hepatitis viruses A, B, C, D and E. Coxsackie B virus may cause an increase in early spontaneous abortions and rarely, fetal myocarditis; echoviruses do not seem to damage the fetus; measles and mumps may cause increased early and late fetal death and neonatal measles or mumps. The viruses affecting the nervous system may increase early and late spontaneous abortions and, rarely, cause severe damage to the fetal brain. Hepatitis B virus has a high rate of vertical transmission causing fetal and neonatal hepatitis. Hepatitis A, C and E are rarely transmitted trans-placentally; if transmitted, they may cause hepatitis. There is no evidence that immunization in pregnancy against these diseases (with attenuated viruses) may adversely affect pregnancy outcome.

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Keywords: Intrauterine infections; Pregnancy outcome; Perinatal effects**Contents**

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1. Introduction

There are several infectious agents that have a high potential to cause significant fetal damage such as rubella virus, cytomegalovirus, varicella zoster virus and *Toxoplasma Gondii*, while others that are less noticeable in pregnancy, seem to have significantly less ability to damage the fetus. In this review, we will discuss the viruses that have little in common except that after infecting pregnant women they may cause fetal or neonatal damage. Their overall risk to pregnancy outcome seems to be low, and therefore their role as possible teratogens is often overlooked. This review is a summary of the relevant literature, especially in the English language, discussing two viruses affecting the nervous system: poliomyelitis and encephalitis viruses, and several other viruses: coxsackie, echo, mumps, measles and hepatitis viruses. In spite of the advances in immunization, there are still countries with poor immunization programs where many of these infections are still common and may affect pregnant women. The discussion will be divided into effects on adults, effects on pregnancy outcome, on the fetus and neonate, and, whenever appropriate, effects of immunization.

2. Viruses affecting the central nervous system

2.1. Poliomyelitis

2.1.1. Effects on adults

Poliomyelitis is a highly contagious, sometimes fatal, acute viral infection that affects motor neurons and can produce permanent muscle weakness, paralysis and other symptoms. It produces a wide range of clinical illness, from none to rapidly progressive paralysis and death. Poliovirus is a RNA virus of the enterovirus group. The infection spreads by swallowing contaminated material; it spreads from the intestine to the parts of the brain and spinal cord that control muscle activity.

Today, because of extensive vaccination, polio outbreaks have largely disappeared, and most doctors have never seen a new polio infection. The Western hemisphere was declared polio free in 1994 [1]. However, new cases are still known to occur mainly in third world countries. Some of these cases are related to possible transformation of the oral polio vaccine [2]. Hence, global eradication has not yet been achieved. Less than 1% of infected people develop any symptoms. Of those with symptoms, 90% simply have fever, mild headache and sore throat. The minor-

ity have more serious symptoms (major polio). Symptoms that appear 7–14 days after infection are more likely in older children and adults, and are more severe in pregnant than in non-pregnant women [1,3]. They include fever, severe headache, a stiff neck and back and deep muscle pain. Diagnosis is confirmed by identifying poliovirus in a stool sample and by detecting high levels of antibodies to the virus in the blood [1].

2.1.2. *Effects in pregnancy*

Reports on the transplacental effects of poliomyelitis in pregnancy were published before the era of widespread immunization. Often, perinatal transmission of the virus was observed when maternal infection occurred late in pregnancy [4]. These infections were associated with increased rate of spontaneous abortions and stillbirths and with paralysis of the newborn infants (congenital polio). Although it is impossible to calculate the exact rate of fetal infection, it seems to be low.

A possible association of intrauterine polio infection with schizophrenia was raised several years ago. This association was mainly drawn from the rate of schizophrenia and affective disorders in the adult population decreased in many countries after the initiation of effective polio immunization. This implies a possible association between in utero exposure to poliovirus and later development of this disease. Suvisaari et al. [5] followed all patients born between 1951 and 1969 with discharge diagnoses of schizophrenia ($N = 13,559$) as identified from the Finnish Hospital Discharge Register. Using a Poisson regression model they found an association between the occurrence of maternal poliomyelitis in pregnancy 5 months before birth and an increase in the rate of schizophrenia in their offspring. According to this study, second trimester fetal exposure to poliovirus may be a risk factor for the development of schizophrenia in adulthood. On the other hand, such an association was refuted by Cahill et al. [6]. The authors calculated the rates per 10,000 background population of poliomyelitis cases and the rates for schizophrenia ($n = 6078$) and affective psychosis ($n = 3707$) for the years 1930–1964. They found no association of the poliomyelitis epidemic to subsequent development of schizophrenia or of affective psychosis [6]. Therefore, the evidence that poliovirus may be a risk factor for development of schizophrenia in adulthood is inconclusive.

2.1.3. *Immunization in pregnancy*

Polio is best prevented by vaccination. There are two types of polio vaccines. The Salk vaccine was the first to be approved in 1955. It is made from completely inactivated polio viruses. The second is oral polio vaccine (OPV), also known as the Sabin vaccine. It is made from weakened polio virus and was introduced in 1962. The vaccines immunize against all three wild virus types. Both types of immunizations are used in many countries today [1,7].

The use of polio vaccine raises the question whether it can adversely affect the fetus if given during pregnancy. The Collaborative Perinatal Project [8] studied pregnancy outcome of 1628 women who were given *live* poliovirus vaccine during the first 4 months of pregnancy and 3059 women who had been given *live* polio vaccine any time during pregnancy. In addition,

they reported on the pregnancy outcome of 6774 women who were given *inactivated* polio vaccine during the first 4 months of pregnancy and 18,219 women who had been given the vaccine anytime during pregnancy [8]. The frequencies of congenital anomalies or principal classes of malformations were not increased among the children of these women immunized during pregnancy. Similarly, no increase in congenital anomalies was found among 2984 children of women who had been 3–15 weeks pregnant during a Finnish immunization campaign that gave *live* poliovirus vaccine to 94% of adults [9]. There was also no increase in the frequency of stillbirth, neonatal death, prematurity or neurological abnormality among cohorts of women who were in their first, second or third trimester of pregnancy at the time of this immunization campaign [10]. No difference in the frequencies of congenital anomalies or of spontaneous abortions, in comparison to the previous years, was found following an Israeli immunization campaign that provided *live* poliovirus vaccine to 90% of the population, including pregnant women [11,12].

A possible association between maternal immunization with inactivated poliovirus vaccine during pregnancy and subsequent development of malignancies, especially of the neural tissue, has been suggested [13]. This inference is made on the basis of the occurrence of 14 malignancies in 18,342 children (7.6/10,000) as compared to only 10 in 32,555 control children (3.1/10,000). In the offspring of women vaccinated during the first month of pregnancy, the rate was 13.2/10,000. There was no evidence of increase in malignancies among children of mothers vaccinated in pregnancy with *live* polio vaccine. If such an association did in fact exist, it could be attributable to contamination of early batches of the vaccine with SV-40, a potentially oncogenic virus [13]. Current vaccines no longer contain the SV-40 virus, and there was no further demonstration of such an association.

2.1.4. *Conclusion*

Live polio virus, even if it had embryotoxic or teratogenic effects, is no longer relevant as a result of practical extinction of the disease. The attenuated or inactivated viruses used for polio immunization, if given in pregnancy, do not seem to cause any harm to the developing embryo or fetus.

2.2. *Japanese encephalitis*

2.2.1. *Effects on adults*

Japanese encephalitis (JE) is a mosquito-borne arboviral disease of major public health importance in Asia [14–18]. The majority of infections are asymptomatic or undetected; for example, in a survey on 300 American men of temporary residence in Korea, only 1 in 25 infections resulted in symptomatic illness [15]. The principal clinical manifestation of the disease is encephalitis; however, milder clinical presentations, such as aseptic meningitis or a simple febrile illness with headache, are common.

2.2.2. *Effects in pregnancy*

Relatively little is known about the risk of JE acquired in pregnancy and the consequences of intrauterine infection. In a

series of outbreaks in Uttar Pradesh, India, JE infection was documented in nine pregnant women. Four women who acquired JE in the first or second trimester miscarried and JE was recovered from products of conception in two cases. In five women who acquired JE in the third trimester, no adverse outcomes of pregnancy were observed [19]. No other relevant data were found.

2.3. West Nile virus

2.3.1. Effects on adults

West Nile virus (WNV) is a single-stranded RNA flavivirus with antigenic similarities to JE and St. Louis encephalitis viruses. It is transmitted to humans through infected mosquito bites. About 99% of the infected human cases are asymptomatic. First in 1999, and then in 2002, the virus caused epidemics of meningoencephalitis in New York City and in the Pacific Coast, with some pregnant women infected as well [20,21].

2.3.2. Effects in pregnancy

There is little data on effects of WNV in pregnancy. There is a report of one woman who had WNV encephalitis during the 27th week of pregnancy who delivered at term a female infant with chorioretinitis and scarring, cystic destruction of cerebral tissue (as evidenced on MRI of the brain), and laboratory evidence of congenital acquired WNV infection [20,21]. However, this single case does not prove a casual relation between WNV infection and these abnormalities. Until the potential risk of this virus to pregnancy outcome is firmly established the appropriate preventive measures should be taken whenever possible.

3. Viruses generally not affecting the nervous system

3.1. Coxsackie virus

3.1.1. Effects on adults

Coxsackie and echoviruses belong to a class known as enteroviruses. Both viruses may be transmitted to the fetus during delivery in 30–50% of mothers with seroconversion in pregnancy, but the rate of trans-placental transmission, although present, is unknown [22–24]. They are transmitted, like other enteroviruses from person to person orally through the fecal–oral route.

Coxsackie viruses are classified into two large groups with 24 coxsackie viruses in group A, and 6 in group B [22,23]. In adults, these viruses usually produce mild symptoms, and are therefore often clinically unnoticed. The most common clinical expression of the infection is an acute, self limited, febrile illness. The clinical presentation may be of myocarditis and pericarditis, pleurodinia (Bornholm disease), exanthemas or enanthemas, hand foot and mouth disease, herpangina, acute hemorrhagic conjunctivitis and sometimes aseptic meningitis or encephalitis.

3.1.2. Effects in pregnancy

3.1.2.1. Type 1 diabetes. Coxsackie virus infections in pregnancy have been associated in several studies with increased

rate of insulin dependent diabetes mellitus in the offspring. A prospective study from Finland showed [25] that intrauterine exposure to coxsackie B virus (CBV) and other enteroviruses, with serologically verified infections, were almost two times more frequent in children that developed insulin dependent diabetes mellitus (IDDM) than in siblings who remained non-diabetic. In a similar study in Sweden [26] sera from 55 women whose infants developed diabetes were tested retrospectively for IgM antibodies for coxsackie B2, B3 and B4. Positive serology was found to be three times higher in frequency in comparison to a group of matched controls, but no differences were found when serology for herpes, mumps and toxoplasmosis was tested in the same sera (27). Similarly, Clements et al. [28] found that in 14 children with early onset type 1 diabetes, 9 were positive for enterovirus RNA, and of these, 6 were positive for coxsackie B3 and B4. Viskari et al. [29] found a higher percentage of women who had in pregnancy IgM antibodies against coxsackie B3, B5 and A11 when their children developed diabetes before 15 years of age in comparison to controls. In contrast to these studies, Fuchtenbusch et al. [30] in a more recent prospective study in Germany, followed up 28 infants of diabetic parents from birth to the appearance of islet auto-antibodies, in comparison to 51 offsprings born to diabetic parents that did not develop auto-antibodies, and found no difference in the rate of coxsackie B3, B4 and B5 infections among these two groups. Similarly, no differences were detected in the antibody levels of maternal serum during pregnancy and at birth. In light of these conflicting studies, it is difficult to relate maternal coxsackie B infection in pregnancy to fetal or neonatal pancreatic damage that will ultimately result in type 1 diabetes mellitus. If such a relation exists, it is rare.

3.1.2.2. Placental infection. Only few reports described placental infection with coxsackie virus. Infection of the placenta, localized mainly to the Hofbauer cells, syncytiotrophoblastic and cytotrophoblastic cells of the terminal villi, was found by in situ hybridization in six of seven newborn infants that had severe respiratory failure [31]. One infant died in the first day of age and the other six developed severe central nervous system sequelae, with subsequent neurodevelopmental abnormalities, mainly mental retardation. No such placental infection was found in 10 normal children.

A recent study by Satosar et al. [32] found that in 60 placentae obtained from cases with fetal or neonatal death or severe neonatal morbidity, coxsackie virus was detected in 22, while no infectious agent was detected in any of 17 control placentae. These studies emphasize the pathogenic role coxsackie virus may have in many pregnancies at term, inducing perinatal death or morbidity.

3.1.2.3. Fetal loss. Axelsson et al. in Sweden [33] looked at the rate of CBV infection in pregnancy in 97 women with miscarriage (80 in the first 12 weeks) in comparison to 113 control women (100 in the first 12 weeks) undergoing voluntary interruption of pregnancy at similar gestational weeks. They studied the levels of maternal IgM antibodies of CBV types 1–5 as evidence of recent infection in pregnancy and found that of 80

women who experienced miscarriage before the 13th week of gestation, 34 (42%) had positive CBV-IgM. This was significantly higher than the rate found in the control women, which was only 18%. There was no difference in the rate of CBV infection between the women in these groups if miscarriage occurred between 13 and 27 weeks [33].

3.1.3. *Effects on the fetus*

3.1.3.1. *Effects on the fetal heart.* The first reports on the effects of coxsackie virus in pregnancy described outbreaks of neonatal myocarditis caused by coxsackie B virus, which seems to be the most common clinical expression of neonatal CBV infection [21]. Indeed, maternal CBV infection during pregnancy may increase the rate of cardiac anomalies. In a study published in Russia by Koro'lkova et al. [34], 62 children with various types of congenital heart disease and 100 normal children were examined, their age ranging from 5 days to 6 years. The presence of coxsackie A and B viruses was studied by immunofluorescence in urine sediment cells in 32 children with congenital heart disease and in 69 controls. Coxsackie A and/or B were found in 84.4% of children with congenital heart diseases versus 7.7% of the controls. When using other indicators of intrauterine enterovirus infection, 93.5% of children with congenital heart diseases were positive in contrast to only 21.9% of the controls. There was no significant difference between the groups in the rate of coxsackie A virus infections, and none of the 20 serotypes studied was detected at a predominant rate. The main difference was in the CBV serotypes, of which coxsackie virus B3 was recovered particularly frequently. This seems to be an important study associating maternal CBV infection in pregnancy with congenital heart disease, but we should remember that the presence of virus was studied in only half of the children, and it is impossible to know from this study how many of the infected children were, indeed, infected prenatally. Similar results were previously observed by Brown and Karunas [35] in a study on the association of maternal enteroviruses infection in pregnancy and congenital anomalies. They studied antibodies in sera from 630 women who delivered infants with congenital anomalies and in 1164 control mothers who delivered normal infants. The general rate of enterovirus infection was similar in both groups, but a significantly higher rate of infections with coxsackie B3 (14/139 versus 7/262 in controls) and B4 (27/133 versus 29/262 in controls) was found in mothers of children with congenital heart disease. Offspring of mothers who had serological evidence of infection with more than one type of CBV had a higher rate of cardiac anomalies than mothers infected only by one virus.

3.1.3.2. *Effects on other fetal organs.* There is conflicting data regarding the possible association of CBV and major congenital anomalies. Evans and Brown [36] reported that the rate of maternal infection during pregnancy with six strains of CBV and of coxsackie A, as well as other viruses, was higher among mothers of offspring with congenital anomalies in comparison to mothers of normal children. Of 274 pregnant women tested for viruses before or during pregnancy, the rate of positive antibodies for

coxsackie B virus was similar among mothers having infants with congenital anomalies (126 mothers) and mothers having normal infants (135 mothers); however, in 30 of the mothers of malformed infants there was evidence of infection during pregnancy as opposed to only 19 in the mothers of normal infants, with the main difference being in coxsackie A or B viruses. The authors therefore related the evidence of infection during pregnancy with these viruses as a sign of their possible involvement in the etiology of birth defects.

In a recent study from Slovakia published by Molnarova et al. [37] sera from 189 newborns with orofacial clefts and from their mothers were studied for the presence of neutralizing antibodies to six types of coxsackie B and two types of coxsackie A viruses, in comparison to control healthy newborns. No difference in the percent of infants and mothers with positive antibodies was found between the groups, implying no association between orofacial clefts and maternal coxsackie virus infection. This statement has some reservation by the authors as they found in different regions of the country a correlation between the rate of orofacial clefts and anti coxsackie antibodies, and they call for larger studies. In light of these conflicting results, it seems difficult to relate maternal infections with coxsackie B viruses to any type of major anomalies, except the cardiac damage described above.

3.1.4. *Neonatal effects*

There is evidence for transplacental passage of CBV in women infected towards the end of pregnancy. The clinical manifestations may be a severe maculopapular rash and other skin lesions in the newborn infant, pneumonia, myocarditis and meningoencephalitis [27]. This may be a serious and often fatal disease, which can be compared in severity to other severe diseases that may appear in the newborn such as Varicella or Herpes simplex infection [24,38,39].

3.1.5. *Conclusion*

CBV in pregnancy can perhaps damage the embryo and fetus causing fetal and neonatal death, and, apparently also cardiac anomalies. Maternal infection at term can often cause severe neonatal clinical manifestations; however, from the current literature it is impossible to calculate the incidence of these fetal complications.

3.2. *Echovirus*

3.2.1. *Effects on adults*

Echovirus is an RNA virus of the genus *Enterovirus* and the family Picornaviridae. Initially termed enteric cytopathogenic human orphan (echo) virus but later simplified to echovirus, these viruses were considered orphan viruses because their relationship to human disease was unknown, and because they failed to produce diseases in laboratory animals. Echoviral infections occur in all human populations. Transmission and infection occur throughout the year in the tropics and predominantly during summer and fall in temperate regions, with sporadic cases in other seasons [21,22]. Echovirus can cause a number of different diseases including rashes, diarrhea,

respiratory infections, myositis, meningitis, encephalitis and pericarditis.

3.2.2. *Effects in pregnancy*

Echovirus may cause neonatal disease following intrauterine acquisition. Dissimilar manifestations in infected premature twins was described, one of the infants had hepatitis and died at the age of 6 weeks from peritonitis and sepsis and evidence of coagulopathy; twin B recovered without sequelae [40].

In another case of intrauterine death in the 29th week of gestation, echovirus 11 could be isolated from the umbilical cord of the fetus and the authors suggested that the echovirus 11 infection was the cause for the fetal death [41]. An additional case was reported recently in a mother and neonate, where the mother also had Bornholm disease [42]. Apart from these case reports we found no evidence that echoviruses can cause, after transplacental transmission, fetal disease or death. In the study by Brown and Karunas [35], no difference was observed in the rate of echovirus (types 6 and 9) infections between 630 mothers of children with congenital anomalies and 1164 mothers of children without anomalies. In contrast, Evans and Brown have shown [36] a higher rate of infections during pregnancy with echo 9 but not echo 6 in mothers of infants with congenital anomalies as compared to mothers of normal children. We found one study where a higher percent of pregnant mothers whose children developed IDDM had positive IgM antibodies against echovirus 11 in comparison to mothers of non-diabetic children (6.2% versus 3.7%, $p < 0.05$) but this was not described by others [29].

3.2.3. *Conclusion*

Although several case reports describe severe fetal damage and fetal death, there seems to be insufficient data to correlate echovirus infection with deleterious effects during pregnancy.

3.3. *Measles*

3.3.1. *Effects on adults*

Measles (rubeola) is primarily a respiratory viral infection clinically different from Rubella, which is not discussed here. The main clinical symptoms are: irritability, runny nose, red eyes, cough and high fever, appearance of a typical rash and Koplik's spots, that are grayish white dots, usually as small as grains of sand, with a slight, reddish areola; occasionally they are hemorrhagic [43]. They tend to occur opposite the lower molars but may spread irregularly over the rest of the buccal mucosa. They appear and disappear within 12–18 h. As they fade there may remain red, spotty discolorations of the mucosa. Measles can lead to many different complications: croup, bronchitis, bronchiolitis, pneumonia, conjunctivitis, myocarditis, hepatitis and encephalitis. Measles is contagious from 2 to 4 days before the rash appears until its disappearance. Before vaccination became widely available, measles epidemics occurred every 2–3 years, particularly in preschool and school-aged children. A woman who had measles or has been vaccinated passes immunity (in the form of antibodies) to her fetus; immunity lasts most of the first year of life [43].

3.3.2. *Effects in pregnancy*

Measles in pregnancy may cause increased maternal complications and increased early fetal and neonatal loss. Chiba et al. [44] described the results of a measles outbreak in Sendai, Japan, from the late 2000 to early 2001 with eight women being infected during pregnancy, four of them before week 24 and the other after week 25. Three of the four cases with infection before 24 weeks of gestation ended in sudden spontaneous abortions or stillbirth directly related to the maternal disease, while the other four pregnancies ended in the delivery of live-term infants. Two of the four neonates were diagnosed as having congenital measles with complete recovery [44]. Eberhart-Phillip et al. [45] followed up 58 women with measles in pregnancy and found that 60% were hospitalized for the disease, and 26% had pneumonia. Two (3%) of these women died. In an additional study in Saudi Arabia [46], of 40 women with measles in pregnancy, 32 (80%) were hospitalized; 4 of them had severe pneumonia but none of them died. No such complications were found in 37 women who were not pregnant while having measles. In both studies an increase in the number of spontaneous abortions and stillbirths as well as premature deliveries was reported. It can be summarized from these data that measles in pregnancy is complicated by a very high maternal morbidity and mortality.

3.3.3. *Neonatal effects*

Increased perinatal mortality without any increase in congenital anomalies was described in several studies. Aaby et al. [47] studied the outcome of a severe epidemic of measles in an urban area of Guinea-Bissau. Increased perinatal mortality (15%) was found in infants born to mothers exposed to measles in pregnancy as opposed to only 4% for other children in the community. Similarly, an association of maternal infection with spontaneous abortion and perinatal death was demonstrated in a measles epidemic in Greenland [48]. This conclusion was supported by a retrospective evaluation of 327 pregnancies over a 12-year period, where the miscarriage rate, if measles occurred in the first 2 months of pregnancy, was 50% and, if it occurred in the third month, was 20%. The perinatal mortality rate was 10%. There was no detectable increase in birth defects in this study [48].

3.3.3.1. *Placental infection.* Pathological changes in the placenta were described by Ohyama et al. [49] in a case of monozygotic twins whose mother was infected with measles at 19 weeks of gestation. One of the twins was stillborn and the remaining one was healthy. The placentae of both twins were affected by the virus, with more severe pathological changes in the placenta of the stillborn infant.

3.3.4. *Immunization*

Measles can be prevented by an attenuated virus vaccine that is administered at 12–15 months of age. Indeed, the rate of the disease was drastically reduced with widespread immunization [43,44]; however, immunity persists in only about 80% of adults if immunized at childhood, increasing the chances of women at childbearing age to be infected by measles and hence suffer from possible consequences on pregnancy outcome [44]. Children and

adults who are exposed to measles and do not have immunity may be protected by vaccination within 2 days of the exposure or by passive immunization with gamma globulin within 5 days [43].

In a description of the pregnancy outcome of 37 women immunized during pregnancy by Heinonen et al., no effects were found on the offspring [8]. Despite the lack of evidence for any side effects of the immunization on the fetus, it has been recommended that measles vaccine be avoided during pregnancy since it is a live virus vaccine [43,50,51].

3.3.5. Conclusion

Measles in pregnancy increases the rate of maternal complications and mortality. The virus can affect the fetus, increasing the chances of abortions, early fetal death and prematurity. There are no data pointing to possible teratogenic effects of measles virus in pregnancy. In spite of immunization programs, measles may occur during pregnancy since only in 80% of those persons immunized the immunity persists into adulthood.

3.4. Mumps

3.4.1. Effects on adults

Mumps is an acute infectious disease caused by the RNA paramyxovirus [43]. Although the disease is usually mild and causes fever and painful enlargement of the salivary glands, complications are frequent. About 10% cases can develop aseptic meningitis, which may result in death or disability. Permanent deafness, orchitis and pancreatitis are other possible complications of mumps. About 20% of men who become infected after puberty develop inflammation of one or both testes (orchitis). On healing, the affected testis may be smaller. If both testes are damaged, sterility may result.

3.4.2. Effects in pregnancy

Results of several prospective epidemiologic studies show no increase in the rate of major congenital anomalies among offspring of women with mumps in pregnancy. No increase in major anomalies was found among offspring of 117 of women, of which 24 were infected in the first trimester [52]. The same was true for other smaller cohorts of women who had mumps during different stages of pregnancy [53,54]. In a retrospective study on 510 pregnancies where the mothers were infected with mumps during pregnancy [55] there was no increase in the rate of congenital anomalies among the offspring.

3.4.2.1. Placental infection. Mumps viral inclusions with severe placental lesions were described in three cases of gestational mumps, one spontaneous abortion and two therapeutic abortions [56]. In one of these cases, the authors also found evidence of infection in the adrenal gland of one fetus.

3.4.2.2. Spontaneous abortions. An association between maternal mumps during pregnancy and spontaneous abortions or intrauterine fetal death was observed in several studies, often occurring 2–3 weeks after the onset of maternal disease. Siegel et al. [57] found that fetal death was increased in 33 women who

had mumps in pregnancy (9/33 cases, 27.3%) in comparison to controls (131/1010, 13.0%). In four cases of maternal mumps in pregnancy [58], two women delivered normal infants and two women had spontaneous abortions about a week after the initiation of the disease, making the association plausible. The author found in reviewing the literature 95 cases of mumps in pregnancy, of which 15% ended in spontaneous abortions or stillbirths and 16% had infants with congenital anomalies involving the heart, eyes, ear structures and urogenital system. In one case of fetal death to a mother who had mumps in pregnancy, mumps virus was isolated from the fetus [59]. We should however remember that these data are mainly based on case reports and there was no comparison to controls.

3.4.3. Effects on the fetus

A possible association between maternal mumps during pregnancy and fetal cardiomyopathy, especially endocardial fibroelastosis (EFE), was described by several investigators and refuted by others. Noren et al. [60] studied the skin reactivity to mumps skin antigen in 11 children without evidence of congenital or acquired heart disease and in 19 children with congenital or acquired heart disease, among them 9 with EFE. All children with EFE had a positive erythematous skin reaction. An additional study on 50 children with EFE published by Shone et al. [61] showed that in 91% of children with EFE under 2 years of age there was a positive skin reaction to mumps antigen, whereas this reaction was positive in only 9% of 200 control children; however, this positive reaction had no correlation with the presence of mumps antibodies in maternal serum. Other studies [62,63] found no association between EFE and mumps either from serological studies or from studies of skin tests was found. We may conclude that if there is any risk that maternal mumps in pregnancy will induce fetal endocardial fibroelastosis, it is small.

3.4.4. Neonatal effects

Perinatal mumps infections following vertical transmission from the mother is rare, and apparently with good prognosis. We found three such reported cases [64–66]. These cases were complicated by respiratory distress and pulmonary hypertension, but had good recovery.

3.4.5. Immunization

Mumps vaccine is routinely used by national immunization programs in an increasing number of countries beginning at 12–15 months of age. In countries with high coverage, a rapid decline in mumps morbidity had been demonstrated, and mumps-associated encephalitis and deafness have nearly vanished. There are several strains of attenuated mumps virus that serve for vaccination [67]. In a study performed on five volunteer women scheduled for a second trimester therapeutic abortions, the women were immunized by the Jeryl-Lynn strain of attenuated mumps virus 7–10 days before the interruption of their pregnancy; the placenta and fetal organs were studied for the presence of the attenuated virus. The virus was detected in two placentae but in none of the fetuses [68]. It is, however, possible that the time interval between immunization and virus detection was too short as to enable virus replication in fetal organs.

3.4.6. Conclusion

Mumps infection of the pregnant woman seems to increase the risk of embryonic and fetal death and spontaneous abortions. No association was found between mumps and congenital anomalies, and the studies relating maternal mumps infection to endocardial fibroelastosis in the fetus are inconclusive. Mumps during pregnancy was rare even before immunization, and is even rarer with the widespread use of mumps immunization in childhood.

3.5. Hepatitis viruses

Viral hepatitis (inflammation of the liver) can be caused by different viruses named hepatitis A, B, C, D and E viruses [69]. They all cause acute or short term hepatitis. Hepatitis B, C and D viruses can also cause chronic, sometimes lifelong, hepatitis. Hepatitis B is a DNA virus and the others are RNA viruses. Other viruses can also cause chronic, sometimes lifelong, hepatitis that is sometimes part of a more generalized disease. They are, however, rare causes of the disease.

3.5.1. Effects on adults

Hepatitis A virus (HAV) is classified with the enterovirus group of the Picornaviridae family. HAV is usually a mild illness characterized by sudden onset of fever, malaise, nausea, anorexia and abdominal discomfort, followed within several days by jaundice. Transmission is from person to person by the “fecal–oral” route. The disease is diagnosed by finding IgM-class anti-HAV in serum collected during the acute or early convalescent phase of disease. The vaccine from inactivated HAV can be used for prevention.

Hepatitis B (HBV) is a double-stranded DNA virus of the Hepadnaviridae family. HBV is endemic in parts of Asia where hundreds of millions of individuals may be infected. It is transmitted horizontally by blood, blood products and by sexual transmission and vertically from mother to infant during pregnancy or during labor.

Acute hepatitis B can range from subclinical disease to fulminant hepatic failure in about 2% of cases. The infected individuals develop clinically apparent acute hepatitis with loss of appetite, nausea, vomiting, fever, abdominal pain and jaundice. Some will develop a chronic carrier state. A common complication of chronic HBV infection is liver cirrhosis and hepatocellular carcinoma [69]. The diagnosis of HBV infection is generally made on the basis of serology. Virtually all individuals infected with HBV, either acutely or chronically, will have detectable serum hepatitis B surface antigen (HBsAs). Effective vaccines are available and all individuals at risk for infection should be vaccinated [69]. Passive immunity to people who have been exposed to hepatitis B virus can be provided by parenteral administration of hepatitis B immune globulin.

Hepatitis C (HCV) was discovered in 1989 by investigators at Chiron Inc. HCV is a positive, single-stranded RNA virus in the Flaviviridae family. This virus was considered, prior to its discovery in 1989, as non-A, non-B hepatitis [69].

The virus is transmitted primarily by blood and blood products and rarely by sexual transmission. Transmission from

mother to fetus or infant is relatively low but possible. About 85% of individuals acutely infected with HCV become chronically infected. The diagnosis of hepatitis C is made by history, serological testing and liver biopsy. There is no vaccine for hepatitis C; the only way to prevent the disease is to reduce the risk of exposure to the virus.

The hepatitis D virus (HDV, also called delta virus) is a small circular RNA virus. The hepatitis D virus is replication defective and therefore can propagate in humans only in the presence of hepatitis B infection, and it is transmitted by blood and blood products. The risk factors for infection are similar to those for hepatitis B. Interferon alpha is used to treat patients with chronic hepatitis B and hepatitis D infection.

The hepatitis E virus (HEV), also known as epidemic non-A, non-B hepatitis, is a common cause of hepatitis that is transmitted via the intestinal tract. It is spread most often by contaminated drinking water and occurs mainly in developing countries.

After an incubation period of 2–8 weeks, infected persons develop fever, nausea, lose their appetite and often have discomfort or pain in the right upper abdomen. Most often the illness is mild and disappears within a few weeks with no lasting effects. No vaccine is available.

3.5.2. Effects in pregnancy

3.5.2.1. Undefined Hepatitis virus. We found two reports from the 1960s, where the hepatitis virus was not defined [70,71]. In a prospective study on the offspring of 60 mothers with hepatitis (type unknown) Siegel and Fuerst [70] found no increase in congenital anomalies, and Adams and Combes [71] found no increase in fetal wastage in 34 pregnancies. Low birth weight was found in 37% of infants born to mothers having the infection after 20 weeks of gestation [71]. In a recent study Khuroo and Kamili [72] described, among a cohort of 76 pregnant women with hepatitis, that in 23 (30.7%) the type of hepatitis could not be defined. Severe maternal disease was observed mainly in the women with hepatitis E, and not in the undefined cases.

3.5.2.2. Hepatitis A virus.

3.5.2.2.1. Vertical transmission. Vertical transmission of hepatitis A is considered to be rare [73]. We found two studies reporting on the outcome of 77 pregnancies in women who developed hepatitis A, and they were both negative, with no evidence of vertical transmission to the fetus [74,75]. However, we also found several case reports of vertical transmission of HAV suggesting a low rate of transmission (about 6%, if based on the 4 positive cases out of 77 negative [76–79]). But from the case reports it is difficult to be sure that transmission indeed occurred in utero or during birth, since all infants developed their disease several days post partum.

3.5.2.3. Hepatitis B virus.

3.5.2.3.1. Vertical transmission. Vertical transmission of HBV can occur either prenatally or during birth and is common in countries where a high percent of the population carries HBsAg, especially if infection occurs in the second half of pregnancy [73]. Infants born to 31 mothers who were diagnosed as having hepatitis B during or shortly after pregnancy have been

followed since birth [80]. Neonatal infection occurred in only 1 out of 10 women infected in the first two trimesters but in 16 out of 21 infants exposed in the third trimester. Of the infected babies, 35% were less than 2500 g at birth [80]. Transmission of HBV to the fetus can apparently be reduced by immunization or immunoglobulin administration immediately after birth, as observed by Beasley et al. [81] in a study in Taiwan. They found that administration of hepatitis B immunoglobulin (HBIG) to neonates that were born to mothers HBsAg positive reduced the rate of vertical transmission to 23% in comparison to 91% in the infants receiving placebo.

3.5.2.3.2. Effects on the fetus. Maternal HBV does not increase the rate of major congenital anomalies in the offspring. In a study of 50 pregnancies no increase in congenital anomalies was observed [82]. The authors found a higher incidence of low birth weight and some asymptomatic carriers among infants whose mothers were infected in the last trimester [82]. The presence of Hepatitis Bs. antigen (HbsAg) is considered to be a typical sign of acute, subacute or chronic HB infection and is hence used for the diagnosis of the disease [69]. Zhaomeng [83] studied 96 pregnant women with positive HBsAg titers and found no increase in malformations as compared to a matched control group. Drew et al. found [84] that when any of the parents was HBsAg positive, there was a very high sex ratio in the offspring (60 males and 24 females). However, difference in sex ratio was not supported by other studies.

In a large study by Wong et al. [85], the perinatal outcome during the years 1996–1998 of 824 women with positive HBsAg (hepatitis B carriers) was compared to that of 6281 women negative for HBsAg (controls). This sample size was large enough to detect a 2% difference among the groups in perinatal outcome and a 1% difference in the rate of congenital anomalies. All delivered after 24 weeks of gestation with birth weights above 500 g. The gestational age at delivery and birth weights were similar between the groups. Similarly, the incidence of preterm birth, rate of small for gestational age births, premature rupture of membranes, neonatal jaundice and perinatal asphyxia were similar between the groups. The rate of congenital anomalies and perinatal mortality were also similar. Thus, the presence of HBsAg does not seem to pose any additional risk for the pregnancy outcome [85].

3.5.3. Conclusion

HBV in pregnancy may result in a high rate of vertical transmission to the fetus, causing fetal hepatitis that, if untreated, may become chronic with possible severe consequences. There seems to be no increased risk for major congenital anomalies in the children of women who are infected with HBV during pregnancy.

3.5.4. Immunization of hepatitis B

The available data suggests that immunization does not impose any risk to the developing fetus. No abnormalities were found among the infants of 10 women who were immunized with hepatitis B during the first trimester of pregnancy [86]. An additional study found one spontaneous abortion from 20 pregnancies among 16 women who conceived after in vitro fer-

tilization and were subsequently immunized with recombinant hepatitis B vaccine during pregnancy, including 6 who were vaccinated in the first trimester [87]. No congenital anomalies or abnormalities of growth and development up to 22 months of age were seen among their liveborn infants. In another study, no birth defects were observed among the infants of 72 women given hepatitis B vaccine in the third trimester of pregnancy [88]. Hepatitis B vaccination during pregnancy is also highly immunogenic, and there is passive transfer of protective antibodies to the newborn [89].

Although we found no studies regarding the outcome of pregnancies in women treated with hepatitis B immune globulin during pregnancy, this should apparently impose no problem, as they are mainly IgG antibodies and different types of IgG antibodies are always transferred from the mother to the developing fetus.

Prevention of hepatitis B virus transmission to the fetus: The rate of perinatal transmission of HBV from HBsAg carrier mothers, who were hepatitis Be antigen positive (HBeAg+) or negative, was studied by Wheeley et al. [90] after using either four doses of vaccine alone, or one dose of hepatitis B immune globulin (HBIG) at birth, combined with four doses of vaccine. No evidence of infection was detected in the infants in any of the two treatment groups. Similarly, the rate of intrauterine transmission of hepatitis B virus was significantly reduced among 105 infants whose mothers were carriers of hepatitis B virus and given hepatitis B immune globulin 3, 2 and 1 month prior to delivery [91]. It was also calculated that routine perinatal vaccination in successive birth cohorts to prevent HBV transmission is cost effective and it effectively prevents HBV transmission [91].

3.5.5. Conclusion

Maternal immunization against HBV in pregnancy, as well as immunoglobulin injection, seem to be safe to the fetus and apparently justified.

3.5.5.1. Hepatitis C virus.

3.5.5.1.1. Effects on the fetus. There are few studies and the data are contradictory. In a study by Medhat et al. [92], 48 pregnant patients with acute viral hepatitis, mainly B and C, were evaluated clinically and by abdominal ultrasonography. The percentage of fetal complications and/or losses was higher in patients who had hepatitis C (30.8%) than in those who had hepatitis B (25%). On the other hand, Floreani et al. [93] showed that in anti-HCV positive pregnant mothers, there was no increase in the risk of obstetric complications, and the maternal liver disease did not deteriorate during pregnancy.

3.5.5.1.2. Vertical transmission. Vertical HCV transmission is an infrequent event among mothers that are HIV-negative. It was found to range, in different studies, from 0 to 13.3% of infants [94–100]. The rate of transmission is apparently directly proportional to the level of viremia in the mothers, and the mothers that did not transmit the HCV had low viral load. Very few cases of vertical transmission were described in the absence of maternal HCV RNA [98].

The general rate of transmission among HCV RNA positive and HIV negative mothers seems to be, calculated from these studies, about 4.1% (30/740). In contrast, HCV and HIV positive mothers have a significantly higher rate of transmission and in a study on 22 mothers co-infected with HIV, eight (36%) transmitted the virus to their babies [94]. In another very recent prospective study [101], the authors found an exceptionally high rate of vertical transmission of HCV as 17 neonates born to 54 mothers (31%) who had positive HCV RNA by polymerase chain reaction (PCR), were HCV PCR positive in the first 3 days after birth.

The presence in the newborn of serum HCV RNA immediately after birth has an important diagnostic and prognostic value, as it identifies those newborns that might develop chronic hepatitis C; however, from several studies [94,98,99] it seems that in infants with vertically transmitted HCV, chronic HCV carrier state and chronic viral hepatitis is rare, and many of the infected infants will become HCV RNA negative within the first years of life. No specific damage was described in the neonates.

3.5.6. Conclusion

Vertical transmission of HCV in isolated maternal HCV infection is around 4%, occurs only with positive maternal HCV RNA and with significant maternal viremia. Transmission is apparently much higher in HCV HIV positive mothers.

4. Hepatitis E virus

4.1. Effects on the fetus

Hepatitis E has an increased severity in pregnant women. In a prospective study carried out in Kashmir, India, Khuroo and Kamili identified 76 pregnant women and 337 non-pregnant women of childbearing age with sporadic acute viral hepatitis, half of them with hepatitis E [72]. Pregnancy was associated with a higher rate of severe disease, as 47 of the 76 pregnant women (61.8%), most of them infected with HEV, developed fulminant and sometimes fatal hepatic failure in comparison to only 34 (10.1%) of the non-pregnant women. Fulminant hepatic failure (FHF) caused by HEV is a severe disease with rapid development of cerebral edema and a high occurrence of disseminated intravascular coagulation, which may represent a severe manifestation of Schwartzmann phenomenon [72]. The Schwartzmann phenomenon that may occur after the introduction of any live or dead bacteria or bacterial filtrate is characterized by an immune reaction, which results in blood clots. These clots are particularly common in the kidney, lung, liver, eyes and brain. This intravascular coagulation is readily apparent in an examination of the blood vessels in the sclera of the eyes. In a more recent study from India [102] Kumar et al. followed 28 women who had HEV in pregnancy. Nine (32%) developed FHF with a very high mortality rate. In another study in the United Arab Emirates [103], 12 of 28 (42.9%) women with symptomatic HEV infection in pregnancy developed FHF; 2 mothers died before delivery and 1 died postpartum. Presuming that all these cases were reported only once we compute the rate of FHF at 48% (60/126). It seems therefore that pregnancy imposes a high risk

for HEV positive women, and these women should probably be advised to refrain from pregnancy. A very high rate of preterm labor is also common among these women [102,103].

4.2. Vertical transmission

Transmission rate from mother to fetus of HEV seems to be high, over 50%. Kumar et al. [103] found that of 26 pregnant women with positive HEV-RNA and clinical signs of infection, all infants developed clinical infection and were HEV-RNA positive. Similarly, Kumar et al. described in a different study [102] a mother to fetus HCV transmission rate of 33.3% (6/18 cases). Khuroo et al. [104] studied the infants born to 10 women, HIV negative, infected with HEV in the third trimester of pregnancy, of which 2 died before delivery. Of the eight liveborn infants, six (75%) had serological evidence of hepatitis E infection, five of which had in their cord blood HEV-RNA detected by PCR. Two of the eight infants died in the first 24 h post delivery. Singh et al. [105] described a transmission rate of HEV to the fetus of 50% (3/6 tested cord bloods). Altogether, of 60 HEV infected mothers, the virus was transmitted to 43 fetuses (71.7%).

4.3. Conclusion

HEV in pregnancy, especially in the third trimester, has a higher ability to cause fulminant disease including death, compared to non-pregnant women. Vertical transmission rate is high, exceeding 50%. There is limited data on other complications of pregnancy.

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