Congenital Anomalies and Viral Infections In Infants

The Etiologic Role of Maternal Viral Infections

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■ *Some viruses, such as rubella and human cytomegalovirus, are known to cross the placental barrier and infect the fetus. In other cases of maternal viral infections, such as herpes simplex, evidence for transplacental passage is less convincing and fetal damage or neonatal disease may be coincidental or associated with perinatal infection. Certain cases of fetal or neonatal disease following maternal viral infections may be associated with disease in the mother which affects her metabolic processes or the placenta in such a way as to interfere with development of the fetus and infant.*

The possible effects of transplacental viral infections are several. Fetal loss may occur by means of abortion or stillbirth. There may be infection of the fetus, with clinical manifestations such as rash, or without clinical manifestations. The infant may be born with congenital defects, including such deformities as cataracts, cardiac anomalies, mental retardation or cerebral palsy.

Although a number of maternal viral diseases have been etiologically incriminated in congenital defects, only two—rubella and cytomegalovirus infection—are definitely proved to be associated with anomalies or mental retardation in infants.

VIRAL INFECTIONS during pregnancy, Kibrick[14] has said, may be associated with fetal mortality, intrauterine infections, congenital malformations and perinatal disease, as well as with mental retardation and cerebral palsy. Blattner[1] reviewed the etiologic role of viruses in congenital malformations and suggested that viral infections during pregnancy may lead to anomalies.

Certain viral infections in the pregnant host have been transmitted to the fetus. The mechanisms whereby viruses gain access to the fetus are poorly understood; however, it is reasonable to assume that their presence in maternal blood may be one source of infection, and direct extension of virus from the exterior by way of the birth canal may be another.

The presence of certain types of maternal antibody (IgA and IgG, 7S species) in the newborn indicates that certain large molecules can cross the intact placental barrier. Passively acquired

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antibodies play an essential role in immunity of the neonatal infant but the extent of this profetuses with certain viruses, such as Group B coxsackievirus, rubella and cytomegalovirus, suggests that at least some viruses infecting the mother are capable of crossing the placental barrier. Some of these viruses, such as Group B coxsackievirus and cytomegalovirus, cause little or no illness in the maternal host but severe or fatal disease in the fetus.

Experimental work in which pregnant guinea pigs were inoculated with certain viruses would indicate that the placenta usually acts as an effective barrier against these viral agents.[17] Thus it may be that the transfer of such agents can occur only if there is placental damage.

It would appear that several factors are involved in determining whether or not the fetus will be affected by a maternal infection. The severity of the infection in the mother probably influences the severity of the infection in the fetus or newborn—that is, the more severe the infection in the mother, the more severe will be the infection in the fetus. The type of maternal infection is an important factor; certain viral infections seem to cause a more severe disease in the fetus than they do in the mother. Other infections, which may be severe in the mother, cause only minor clinical manifestations in the fetus or newborn. The length of gestation before infection occurs is also an important factor. It would appear that the fetus would be more severely affected by infection with some viruses early in gestation, whereas infection with other viruses might create a problem regardless of when the mother became infected.

There are adequate data indicating that newborn babies produce viral antibodies under certain conditions but sometimes engender no such response. Protection from disease may or may not be accompanied by the presence of antibodies. Not all the factors that enter into this complex situation are known, but it would appear that immunity involves more than the presence or development of antibodies.[6]

Over a dozen viral diseases occurring during pregnancy may be associated with untoward effects on the fetus or newborn. However, only two maternal viral infections, rubella and cytomegalovirus infection, have been associated definitely with an increased risk of anomalies in infants. Other observed anomalies in infants following maternal viral disease could be coincidental. Certain observed effects on the fetus following these diseases in the mother have been described.

Rubella (German Measles)

The true nature and potential severity of rubella infection in the expectant mother became apparent in 1941 when Gregg,[10] an Australian ophthalmologist, first reported the relationship between rubella in the pregnant woman and the occurrence of congenital malformations in her offspring. The most common abnormalities encountered in children whose mothers had this disease early in gestation include congenital cataract, congenital heart disease, especially patent ductus arteriosus, perception deafness, microcephaly and mental deficiency. Less frequently seen are other conditions such as microphthalmus, buphthalmos, retinal lesions, talipes equinovarus, syndactyly, hypospadias, generalized muscular weakness, cerebral diplegia, cleft palate and dental anomalies. These have been called the rubella syndrome.

In some studies, 50 per cent or more of infants born to women who had rubella during the first four weeks of pregnancy have had severe congenital anomalies. If exposure occurs during the second or third trimester, there is much less risk of the rubella syndrome resulting. However, during the recent rubella epidemic the occurrence of persistent infection in the fetus has been reported when the mother contracted rubella in the second trimester. In such circumstances, the infant may shed rubella virus for many months after birth.

DeKaban and associates[4] showed that the highest incidence of five major abnormalities—cataract, congenital heart disease, deafness, microcephaly and mental retardation—results when rubella infection occurs in the first five weeks of gestation.

In 1962 the cultivation of rubella virus in tissue culture by Weller and Neva[28] and Parkman and associates[21] made it possible to carry out virus isolation and serological studies of patients with typical, atypical and subclinical types of rubella. Studies of the nation-wide epidemic of rubella in 1964 have clarified our understanding of the pathogenesis of congenital rubella.

If viremia occurs during pregnancy, the fetus under 12 weeks of age is particularly susceptible to infection, which persists and is present at birth. Clinical manifestations include: (1) Low birth weight; (2) eye lesions, i.e., cataract, glaucoma,

retinitis; (3) deafness; (4) brain lesions associated with microcephaly, meningoencephalitis, hydrocephalus and mental retardation; (5) cardiac defects, i.e., patent ductus arteriosus, ventricular septal defect; (6) thrombocytopenia purpura; (7) hepatosplenomegaly; (8) pneumonitis; (9) jaundice; and (10) bone lesions. Since infants with congenital rubella infection may shed virus from the throat and urine for at least six months after birth, they may spread disease.[16]

In 1958, studies by Krugman and Ward[15] showed that neutralizing antibody to the virus of rubella was present in ordinary gamma globulin; they suggested the relative efficacy of these preparations in the prevention of clinical manifestations of the disease. More recent studies by Krugman[16] and others have yielded information showing less definite effects from the use of gamma globulin. The question of therapeutic abortion in women who develop clinical rubella during pregnancy invariably arises. The decision must be based on many factors and in each case weighed individually. Recent studies have indicated that human gamma globulin may suppress the clinical manifestations of rubella in the mother without preventing the occurrence of viremia. Studies to determine whether gamma globulin does or does not reduce the risk of congenital malformations, stillbirths or abortions are in progress by Dr. John Sever of the National Institutes of Health.

Cytomegalic Inclusion Disease

The clinical entity referred to as cytomegalic inclusion disease, or generalized salivary-gland virus disease, has become a more familiar problem within the past decade since exfoliative cytologic studies and techniques for isolation of the causative virus have resulted in the recognition of cases during life. Human cytomegalovirus appears to produce no demonstrable illness in the mother, yet may give rise to severe, frequently fatal disease in the fetus and newborn.[32]

In retrospect, a stillborn with inclusion-bearing cells in the liver, lung and kidney reported by Jesionek in 1904 probably represents the first example of generalized cytomegalic inclusion disease.[11]

The distinctive morphologic feature of cytomegalic inclusion disease is the large inclusion-bearing cell, which may appear in almost any organ. The large intranuclear inclusion is surrounded by a clear halo, which separates it from a distinct nuclear membrane. A cytoplasmic or paranuclear inclusion may be found frequently in infected cells.

In 1953, Fetterman[8] detected the inclusion-bearing cells in urinary sediment, thereby introducing exfoliative cytology as a diagnostic procedure; and in 1956 Smith,[24] Rowe[22] and Weller[26] isolated the virus from the urine, salivary gland, adenoid tissue and liver of infected infants, introducing viral isolation techniques for diagnosis.

The clinical manifestations regularly observed in patients with this disease are most clearly defined as they appear in the newborn, premature infant. Prominent features in the typical cases include jaundice, hepatosplenomegaly, petechiae and microcephaly as well as the laboratory findings of anemia, hyperbilirubinemia, thrombocytopenia, paraventricular intracerebral calcifications, inclusion-bearing cells in the urine and the presence of virus in the urine and throat swabbings. These findings in 12 infants infected with human cytomegalovirus were summarized by Wright and associates,[32] who emphasized that infection with these agents in utero or in the neonatal period is not necessarily fatal.

The sequelae of such infections may range from recovery to varying degrees of neurologic involvement, including hydrocephalus, microcephaly and cerebral calcifications, usually in association with motor impairment and mental retardation. However in only three of seven patients tested in one series was retardation considered severe at one year of age.[32] The persistence of hepatosplenomegaly and the variety of tissues in which inclusions have been found suggest that the sequelae of this disease may not necessarily be limited to the central nervous system. In some cases, the clinical histories resembled those of neonatal hepatitis, and virus has been grown from the liver in such cases.[27]

A long-term evaluation of the physical and mental development is needed to define the prolonged effects of congenital infection with human cytomegalovirus. Such a study is under way in several centers.

Other Viral Diseases Possibly Associated With Anomalies

Herpes Simplex

The primary infection with herpes simplex usually occurs between six months and three years of age. Infection with herpes simplex virus is extremely common in older children and adults and

is usually inapparent or associated with a vesicular infection of the skin or mucous membranes. However, if newborn infants should become infected with this agent, a severe disseminated disease characterized by extensive infection of many organs, primarily the liver, lungs and adrenal glands, occurs within the first week of life and usually results in death.[31]

Infants with this disease have fever, profound weakness, skin vesicles, jaundice, hepatosplenomegaly, ulceration of the esophagus, dyspnea, cyanosis and bleeding tendencies associated with thrombocytopenia.[23,31]

Pathologically, affected organs are riddled with pale, yellow, firm, necrotic nodules measuring a few millimeters in diameter. Characteristic inclusion-bearing cells (Cowdry Type A) may be seen microscopically in the infected organs.

Transmission of infection from the mother to the infant most frequently occurs during passage through the birth canal or by contact after birth, but transplacental infection also is known to occur.[23]

Generalized disease in the newborn infant due to herpes simplex virus is so rarely encountered and has so wide a spectrum of clinical manifestations that this diagnosis is usually not considered, even in infants with severe disease.

For the infants who recover the prognosis is poor. Chorioretinitis and blindness as well as severe mental and psychomotor retardation are the rule in surviving infants with this disease.

Although rare, generalized herpes simplex should be considered in severe illness of the newborn when symptoms suggest an infectious disease.

Coxsackievirus Group B Infections

Coxsackieviruses Group B types one to five have been established as etiologic agents of severe, often fatal illness in newborn infants in which there is encephalitis and extensive focal myocarditis.[30] The liver, pancreas, adrenal glands and other abdominal organs may also be affected. The mother may have had a pleurodynia-like illness late in pregnancy and this, along with early signs of clinical illness in the infant, suggests intrauterine infection.

The clinical manifestations include a biphasic course, feeding difficulty, respiratory distress, lethargy, cyanosis, hepatomegaly and jaundice. Collapse and death may occur within a few days, or apparent recovery may occur over the succeeding few weeks. Myocarditis has been the most constant pathologic finding, although meningoencephalitis and hepatic necrosis are also frequently observed postmortem.[9]

Known cases of this disease in newborns may be divided into two groups. Infants may have extremely severe and generalized disease associated primarily with myocarditis, encephalitis, vascular collapse and death, or they may have minor illnesses, such as aseptic meningitis, and recover. The data on long-term follow-up of such patients is scanty, and it is possible that certain cases of chronic myocarditis or mental retardation appearing in later life are sequelae of early infection with group B coxsackievirus.[14]

Rubeola

There are several recorded cases in which maternal measles has been followed by the birth of defective children. The observed malformations have included mental retardation, congenital heart disease, deafness, cleft lip, talipes equinovarus and genu valgum. Since virus was not isolated in those cases, the possibility exists that infection with rubella may have been a factor, or they may have occurred by chance. Packer[20] showed that when measles was present at birth, the disease was usually in the same stage in the infant as it was in the mother. This suggests that the virus of measles can cross the placenta at any stage of gestation.

Mumps

Evidence has been accumulating for a number of years that infection with the virus of mumps occurring in early pregnancy can affect the fetus adversely; spontaneous abortion and stillbirth have been reported.[1] Congenital defects described following maternal mumps include spina bifida occulta, urogenital tract deformity, external ear anomalies, hypospadias, heart lesions and meningoencephalitis. These defects may have occurred by chance. Apparently no case of mental retardation following maternal mumps has attracted attention.

Varicella and Herpes Zoster

Although varicella is frequently transferred from a mother with the disease to the fetus in utero, no case of congenital defect or mental retardation in the infant has been reported. Varicella has been present at birth or has occurred

as late as the tenth day of life when the mother has the disease at the time of delivery. In fatal cases of congenital or early neonatal varicella, postmortem examination has revealed a generalized widespread infection with focal areas of necrosis and hemorrhage in many organs.[1] Duehr[5] described congenital cataracts in two patients whose mothers had herpes zoster (a virus which is considered identical to the chickenpox virus) within the first trimester of pregnancy. Other anomalies included mental retardation, microphthalmus and talipes equinovarus. It is interesting that these anomalies are similar to those produced by rubella.

Smallpox

The virus of smallpox crosses the placenta and thus may be the cause of disease in the fetus while in utero, or following birth if the disease is still active in the mother.[18] Spontaneous abortion is common because of the severity of the disease in the mother. Rarely the infant may be born with clinical evidence of the disease or with congenital malformation such as cataract or hydrops fetalis. No report of mental retardation has come to my attention.

Hepatitis

Stokes and coworkers[25] presented evidence that neonatal hepatitis could be associated with transmission of virus across the placenta. In some cases, consideration of the incubation period pointed to intrauterine infection, and in one case the presence of virus was demonstrated by the inoculation of mother's and infant's blood into human volunteers, disease resulting. The relatively low incidence of infectious hepatitis in pregnancy has made it difficult to obtain accurate data concerning the effect of these agents upon the fetus. In 1951 Kass[12] described a decidedly hydrocephalic and microphthalmic infant whose mother had had infectious hepatitis in the second and third months of pregnancy, and Blattner[1] reported the case of an infant (observed by Hellbrügge) born to a mother who had had hepatitis during her fifth week of pregnancy; this infant showed signs of physical and mental retardation at three months of age, as well as eye disease involving the iris, choroid and optic nerve.

Influenza

The various forms of influenza are often severe in pregnant women and the incidence of abortion, stillbirth and premature birth has been considered high during epidemics. Kaye and associates,[13] in a review of congenital anomalies over a five-year period in Chicago, noted three infants with multiple defects and mental retardation whose mothers in their first trimester had had an illness described as severe influenza, due to "Virus-X," with high fever. A more recent study prompted by the appearance of Asian influenza in California indicated there was no significant difference in incidence of anomalies in infants whether the mothers had or had not been infected during pregnancy.[29] Two infants whose mothers had been infected were anencephalic, however.

Arthropod-Borne Encephalitides

Eichenwald and Shinefield[6] pointed out that of the arthropod-borne (Arboviruses) encephalitides, western equine encephalomyelitis (WEE) and eastern equine encephalomyelitis (EEE), are the only two types of this infection of clinical importance during the newborn period in the Northern Hemisphere. Infection with viruses causing St. Louis encephalitis and Japanese B encephalitis is virtually nonexistent during the neonatal period. Newborn infants may acquire WEE by the transplacental transmission of the agent or be infected by the bite of infected mosquitoes. Many of the manifestations of central nervous system damage caused by this virus, such as seizures, motor impairment and mental retardation, may not become clinically apparent until some months after the initial infection.

Other Viral, or Suspected Viral, Infections

Spontaneous abortion, stillbirth, premature delivery and congenital infection have been commonly associated with poliomyelitis during pregnancy. Bowers and Danforth[2] followed the course of 24 full-term infants whose mothers had poliomyelitis during pregnancy and presented data suggesting these babies showed a significant retardation in general development and birth weight.

The cause of infectious mononucleosis is unknown but is suspected to be viral. Cases of infectious mononucleosis have been known to occur during pregnancy, and newborn infants of the affected mothers have been observed and followed, but no definite evidence suggesting mental abnormalities in these children has been reported.[1]

Day[3] and other investigators have suggested "clustering"—that is, increased incidence in time and space—of certain diseases due to chromo-

somal abnormalities, such as mongolism. Nichols[19] has shown that certain viruses can produce several changes in chromosomes. It is not known at present whether there is any association between maternal viral disease and chromosomal abnormality in the offspring.

Prevention of Viral Diseases

The scope of this report is too limited for an extensive discussion of preventive measures for viral diseases. Chemical substances known to have some antiviral activity might be considered useful if begun soon after birth; however, associated side effects might rule them out. One of the halogenated pyrimidines, IDU (5-iodo-2′-deoxyuridine), may become useful in the systemic treatment of congenital herpes simplex or cytomegalovirus infections, both of which are desoxyribonucleic acid viruses and cause severe disease and mental retardation; however, subsequent dangers due to the use of such a drug might be so great as to prevent its use. Evidence has recently been presented which indicates this substance becomes incorporated in cellular DNA, causing a sensitization to ultraviolet light and x-ray, and hence might theoretically lead to mutations of possible oncogenic nature.[7]

The practicality and success of the immunological approach to the control of viral diseases may be exemplified by the remarkable reduction in the incidence of smallpox and poliomyelitis since widespread use of specific antiviral vaccine. Since infants may be born with clinical viral disease or the mother might have had a viral disease for which no vaccine is available, the immunological approach is not appropriate in all situations.

The use of gamma globulin in the newborn when a viral disease is present or suspected is controversial. Use of it in diseases such as generalized herpes simplex, hepatitis and varicella has been suggested, but whether it can prevent resulting complications such as mental retardation is not known.

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