Fetal Abnormalities of Viral Origin*

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The high incidence of acute infections known to occur in pregnant women contrasts with the relative rarity of fetal damage and attests to the efficiency of the mechanisms by which the fetus is protected *in utero*.

The events shown in Fig. 1 summarize some of the obstacles which a virus must overcome in order to reach the fetus and produce defects. An effective exposure is required to allow the virus to multiply locally in the maternal tissues at the portal of entry. If a viremic phase results, the virus becomes disseminated and the placenta may be infected; depending on the type of infection, placental damage may or may not result. If the virus successfully crosses the placental barrier, the fetus may become infected either by way of fetal viremia or by contiguous spread through the membranes. Since maternal viremia is necessary to initiate this chain of events, the fetus is naturally protected against viruses which seldom invade the blood stream. Most of the viruses causing respiratory diseases fall into this category. The maternal immunologic system provides significant protection by circulating antibodies stimulated by earlier natural or vaccine induced infection. Even if the mother is susceptible and the infection is associated with viremia, the virus may still be effectively stopped by the placental barrier; this has been shown to occur commonly in both rubella and cytomegalovirus (CMV) infection. If, on the other hand, the virus reaches the fetus, to produce a teratogenic effect the virus must have a delicately controlled pathogenicity allowing a chronic infection to be established compatible with a period of continued growth and development. Only two or perhaps three human viruses have been documented to have the ability to produce such infections. These include rubella virus, human cytomegalovirus, and, possibly, herpesvirus hominis (herpes simplex virus).

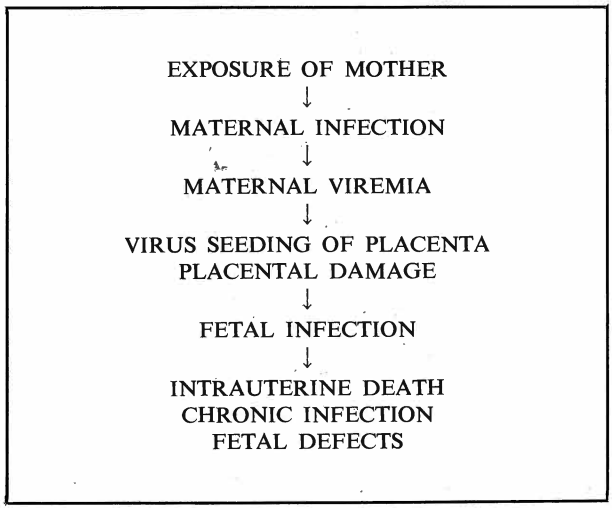

Fig. 1—Events leading to fetal infection and disease.

Of these three human viruses, the teratogenic effects of herpes simplex virus are the least documented. There are 5 reports in the literature suggesting that genital herpes infections acquired early in pregnancy may be associated with congenital malformations. Defects seen in these 5 infants included microcephaly, microphthalmus, and chorioretinitis. Skin lesions were present either at birth or soon thereafter in 3 cases and encephalitis was present in 1 instance. Investigation of the infants with microcephaly for other possible infectious etiologies including cytomegalovirus and toxoplasmosis infection gave negative results. The association of herpes simplex virus with eye and central nervous system (CNS) defects in these cases is highly suggestive that this virus may on occasion be teratogenic; the role of herpes simplex virus in this regard deserves further investigation (Nahmias, *et al*, 1970).

As the result of a decade of intensive interest, rubella represents the most adequately studied

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congenital infection producing fetal defects (Krugman, 1969). It also represents the only teratogenic virus infection currently controllable through the use of vaccine.

Rubella is recognized to occur every year in sporadic outbreaks covering restricted areas. Since 1928 major epidemics of the disease involving the entire country or large sections of the country have occurred at 6- to 9-year intervals. Rubella shows the same prominent seasonal pattern of other diseases transmitted by the respiratory route. The maximum incidence of the disease occurs during the winter and spring months, with very low rates in summer and fall. In a nonepidemic year, it has been estimated that the occurrence of rubella in pregnant women is in excess of 8/10,000 pregnancies. In an epidemic year, this rate may increase 30 to 40 times.

The clinical features of natural rubella virus infection vary from the clinically inapparent to an illness of sufficient severity to be confused with measles. Children before the age of puberty tend to have a mild illness consisting typically of 3 days of low-grade fever, seldom exceeding 101°F, rash, and generalized lymphadenopathy. Nodes are especially prominent in the posterior cervical region. In adults, particularly women, the illness is often more severe. The earliest evidence of infection is lymphadenopathy. The nodes may be tender and the enlargement often persists for several weeks after the onset of symptoms.

The rash is variable in appearance. Ordinarily, it first becomes apparent on the face and spreads rapidly to the trunk and upper extremities. It may have begun to fade on the face by the time it becomes fully developed on the lower extremities. Prominent respiratory tract symptoms do not occur. Women with rubella sometimes also complain of headache, malaise, myalgia, painful gums, and paresthesias, particularly of the hands.

Rubella is the only viral infection in this country which is frequently associated with arthralgia and arthritis. Age and sex have a marked effect on the frequency and severity of these symptoms. In a recent retrospective survey following an epidemic, 25% of prepubertal children experienced joint-related symptoms. After puberty there was a sharp increase in the incidence of arthralgia and arthritis, and with increasing age between menarche and menopause the frequency and severity of involvement increased progressively. Commonly the joint symptoms followed the rash by several days, although in some instances arthritis preceded the rash or was delayed until several weeks after the onset of infection. The joints involved, in order of frequency, were the proximal interphalangeal joints, the knees, wrists, ankles, and the metatarsophalangeal joints. Symptoms ordinarily subsided in 1 to 14 days but some patients, notably older women, experienced recurring symptoms lasting for a year or more. Even in such instances symptoms have cleared and there has been no residual deformity. There is no evidence that these reactions predispose to the development of chronic arthritis.

In the typical case, virus may be recovered from blood and respiratory secretions one to one and a half weeks prior to the onset of rash. Viremia disappears shortly after the onset of rash in association with the appearance of circulating antibodies. Presence of virus in the respiratory tract diminishes more slowly; virus may continue to be recoverable for several weeks. Neutralizing and hemagglutination-inhibiting (HAI) antibodies develop promptly after the exanthem appears and persist for years, probably for life. The CF antibody response is slightly delayed and may decline over a period of years. The widespread availability of the HAI test has made the rubella serodiagnosis of critical cases available to everyone. Establishing an accurate diagnosis is nowhere more important than in the instance when a pregnant woman is exposed to rubella. Under such circumstances, an initial serum specimen should be obtained as soon as possible after exposure and tested for antibodies to determine the immune status of the patient. Subsequent samples should be collected in early convalescence if disease develops and in asymptomatic patients at 4 and 6 weeks after exposure. These later samples tested in parallel with the earlier specimen will document if infection has occurred.

In 1940, a communication appeared in a prominent medical journal protesting interest in rubella as inappropriate since it was "an entirely inconsequential disease." This misconception was laid to rest within the next year by the astute observations of an Australian ophthalmologist. This was the contribution of the late Sir Norman Gregg, who opened the field of viral teratogenesis as a result of his discovery of the association between maternal rubella, congenital cataract, and heart defects. Over the years since Gregg's original observations, it has become apparent that virtually any organ system of the developing fetus may be damaged.

The fetal infection may be severe enough to

cause spontaneous abortion or stillbirth. Congenital involvement often present in the newborn period included deafness, heart disease, retardation, meningoencephalitis, microcephaly, eye defects, including congenital cataract, retinopathy and glaucoma, purpura, anemia, hepatosplenomegaly with hepatitis and jaundice, pneumonitis, and bone lesions.

The earlier in pregnancy maternal rubella occurred, the more likely it was that the defects would be multiple and severe. Follow-up data indicated that infection during the first 2 months of gestation was associated with the highest incidence of heart, eye, and CNS defects; fetuses infected in the 3rd month had significantly fewer heart and eye defects. All types of malformations declined in those babies who had been infected during the 4th month (Cooper, *et al,* 1969). It has been estimated that the chances of anomalies when maternal infection occurs during the first month is in excess of 50%, in the second month about 22%, and in the 3rd through 5th months, 6% to 10%.

In the pathogenesis of congenital rubella, viral invasion of the placenta occurs during the period of maternal viremia. Replication of virus in the placenta produces focal areas of mild inflammatory response and scattered damage of the endothelium of the chorionic blood vessels. Extension of the infection to the fetal circulation permits the virus to reach the developing organs where a persistent infection ensues. This infection may be localized or widely disseminated throughout the fetal tissues. Virus shedding in pharyngeal secretions and urine and the presence of virus in the tissues can be demonstrated throughout the neonatal period; in those infants with severe rubella defects, particularly, virus shedding may continue sporadically into the second year. The presistence of virus is of epidemiological importance since rubella infected infants can transmit their infection to nursery personnel and other contacts; thus it is important to limit the contact of such infants with pregnant women in the hospital and after discharge.

Antibody responses in maternal rubella, as with most infectious diseases, consist of the early appearance of transient IgM antibody, promptly followed and eventually replaced by the IgG class of antibodies. It is the latter which are responsible for the long-term persisting rubella antibodies. The situation in the infected fetus is more complex. Maternal IgG is transplacentally transferred. The infected fetus begins to produce his own immune substances, in the form of IgM antibodies, at some period during the second trimester. At birth the titer of antibodies in maternal and infant sera is very nearly the same. The infant's antibodies are made up of both transplacental IgG and endogeneous IgM. As many as 80% of rubella infants will have an elevated IgM serum protein fraction during the neonatal period. During the first year of life, passively acquired IgG declines. The production of infant IgG appears during the early months of life, and late in the first year replaces IgM as the predominant rubella antibody.

At the present time, short of therapeutic abortion, there are two methods for averting congenital rubella: (1) passive immunization of exposed pregnant women using commercially available immune serum globulin (gamma globulin); and (2) the use of live attenuated rubella virus vaccine for active immunization of nonpregnant subjects.

Gamma globulin has been commonly used for many years for the prevention of rubella infection in exposed pregnant women. The efficacy of this procedure has been a matter of controversy. There is no question that large doses of globulin given *prior to exposure* are effective in decreasing the incidence of infection and the clinical manifestations among those who acquire infection. In the ordinary circumstance in which globulin is used, however, exposure has already occurred several days earlier. In such cases the beneficial effect of globulin is less well documented. In fact, children with rubella syndrome defects have been born to mothers given appropriately timed adequate doses of gamma globulin. Carefully performed virologic studies, designed to mimic the usual post-exposure situation encountered clinically, failed to show protection against experimental infections, although there was some effect in diminishing the duration of viremia. From these data, it is obvious that globulin is unreliable as a measure for the prevention of congenital defects. On the other hand, it is impossible to be certain that globulin, through reducing the duration or level of viremia, might not have some effect in reducing the risk of fetal infection. On this basis, and because it represents the only currently available measure which might be of help in this situation, our feeling is that the continued use of large doses (20 ml of gamma globulin) is justifiable in circumstances where interruption of pregnancy is not desired.

Live rubella vaccines are prepared in cell cultures and induce immunity by producing a modi-

fied rubella infection in susceptible persons (Meyer and Parkman, 1971). The 3 vaccines currently available are produced in duck embryo cells by Merck, Sharp, and Dohme (Meruvax®), in canine renal cells by Philips Roxane, Inc. (marketed by them as rubella virus vaccine, live) and by Parke Davis and Co. as Rubelogen®, and in rabbit renal cells by Smith Kline and French, Inc. (Cendevax®). In children, vaccine induced infections are usually asymptomatic, while adults may develop rubella like symptoms. Such symptoms may consist of an evanescent rash, lymphadenopathy, and transient peripheral nerve and joint involvement. The most troublesome complaints have been related to occurrence of arthralgias, arthritis, and paresthesias; these symptoms follow a pattern of distribution similar to that seen in the natural disease. They appear within 3 to 5 weeks after immunization, but on occasion may be delayed until 8 weeks postvaccination. Reaction rates in women of childbearing age range from 10% to 60% and as in the natural disease are in part related to the age of the woman; reaction rates have been highest in the older age groups. The immunogenicity of the vaccine used also affects the likelihood of reactions. The canine renal cell prepared vaccine which produces higher antibody levels was also responsible for higher reaction rates than vaccines prepared in duck or rabbit cells. The joint manifestations are usually mild; however, occasionally a patient may continue to have residual subjective complaints lasting for weeks or months. Persons with arthritic manifestations have not shown the development of later chronic joint disease.

Rubella vaccines stimulate antibodies in 95% to 100% of recipients between the 2nd and 4th weeks postvaccination. Thus far, these antibodies have been shown to persist without significant decline throughout the 5-year period of observation since the earliest vaccinations were performed.

In the United States, efforts of mass vaccination programs have been directed toward the immunization of children. This approach is designed to reduce the opportunities for spread of virus by decreasing the susceptible childhood population most responsible for initiating and maintaining epidemic rubella. At the same time, the desirability of providing protection for the susceptible adult women is also recognized. Immunization of this group presents special problems. Arthritic reactions are more common in this age range; most important, however, is the risk of immunizing women in unrecognized early pregnancy or women who may become pregnant immediately after vaccination. In such situations, it has been shown that in susceptible women the attenuated virus can produce chronic placental infection which may be transmitted to the fetus. Generally, when vaccinations have been performed early in gestation, therapeutic abortion has been performed. Too few pregnancies have proceeded to term to determine the possible consequences of fetal infection with vaccine virus. Thus it is highly important when vaccinating adult women, to insure that the patient is not pregnant and will not become pregnant for at least two months after immunization. Pretesting of women for HAI antibodies is recommended and will exclude the necessity for using vaccine in immune women.

If vaccines are used extensively and if the immune status of the population can be maintained at a high level, it seems possible that rubella control can be achieved.

In comparison with the abundance of information available about rubella, knowledge of the epidemiology and pathogenesis of congenital CMV infections is limited. Thirty to sixty percent of childbearing age women have detectable antibodies. Infection during the reproductive years may be quite common. Serologic responses occurred in 3% to 5% of pregnant women in two urban centers studied. Information is not currently available concerning the frequency with which maternal infection is transmitted to the fetus. It is also unclear what proportion of fetal infections are (1) inapparent, (2) silent at birth but produce clinical manifestations later, or (3) result in classical cytomegalic inclusion disease. The reason for this poor documentation is in part attributable to the fact that maternal infections are subclinical. Rarely acute CMV infection in the adult may mimic infectious mononucleosis. Diagnosis of maternal CMV infection by virus recovery is hampered by the observation that virus may be shed in the urine for periods up to 2 years following initial infection; thus recovery of virus from a pregnant woman does not necessarily indicate acute disease.

The occurrence of the majority of congenital CMV infection in babies born to young primiparous mothers, suggests that intrauterine infection is most commonly acquired by the fetus during the viremic phase of primary maternal CMV infection. Fetal infection may occur in the first trimester (Davis, *et al,* 1971) and perhaps later in pregnancy as well. As in rubella, it has been shown that placental infection may occur without infection of the fetus.

Congenital CMV infection in 2 siblings born within 8 months of one another has been recently reported (Emil, *et al,* 1970). The possibility of such an occurrence should not be overlooked in the follow-up of women who have borne a CMV affected child.

Adding to the complexity of the CMV problem is the observation that multiple antigenic variants of the virus exist; the significance of this variation in the virus for immunity and the possibility of reinfection is unknown.

The features of classical congenital cytomegalic inclusion disease include, like rubella, defects in CNS, eye, and hepatic and bone marrow function. Microcephaly and hydrocephaly, encephalitis, cerebral calcifications, convulsive disorders, chorioretinitis, blindness, hepatosplenomegaly with jaundice, thrombocytopenia with petechiae, anemia, and interstitial pneumonia all can occur. Unlike the rubella syndrome, cataracts and heart defects are not seen.

As in congenital rubella, virus can be recovered from throat, urine, and blood of affected live born children and from multiple tissues of aborted or stillborn fetuses. Virus recovery from clinical specimens, unless accomplished in the immediate newborn period, cannot be taken as certain indication of an etiologic relationship between defects and CMV infection since these viruses can be recovered with some frequency from urine of asymptomatic children. The demonstration of elevated serum IgM and the persistent occurrence of specific CMV IgM antibodies in the serum of newborn infants provides convincing evidence of intrauterine infection (Sever and White, 1968; Alford, *et al,* 1967).

Aside from the experimental use of chemotherapeutic agents which inhibit replication of DNA viruses in children with the congenital disease, no methods of prevention or treatment are currently available.

What new developments are likely to occur which might be important from the standpoint of congenital infections? Several recent reviews have explored the status of other viral agents in producing abortions, stillbirths, and neonatal disease. It has been speculated on the basis of epidemiologic studies that other agents including varicella, vaccinia, mumps, influenza, and measles viruses may possibly induce fetal defects (Sever and White, 1968; Hardy, 1965). The etiologic relationship of these viruses with congenital defects are not in hand, but with additional study might yet be proven. Perhaps other mechanisms than those active in rubella and CMV infections will be shown important. An even more interesting possibility relates to the cancer virus field. Impressive evidence is available indicating that many tumors of amphibians, birds, rodents, and cats are caused by viruses. The study of animal model systems in chickens and mice indicates that RNA leukemia viruses may be transmitted "vertically," that is, directly from mother to embryo. The incidence of malignant disease in the congenitally infected animal is higher than that seen in the adult host infected by contact. Could such situations exist in man? Enough parallels exist between the human and animal diseases to make this a tantalizing possibility. Perhaps as techniques for searching out human oncogenic viruses become more sophisticated, similar agents may one day be recognized as causing highly important congenitally acquired infections.

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