Viral infections

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Viral Infections

During the past decade, 1966-1976, increasing interest has centred around the effect that infections acquired in pregnancy may have on fetal development and subsequent development after birth. The year 1966 was an important landmark in the study of viral infections acquired in pregnancy for the rubella vaccine trials (reported that year by Meyer *et al*, 1966), signalled the first attempt, by means of active immunization, to prevent the ill effects of a maternal infection upon the fetus. And now in 1976, serious consideration is being given to prevention of another, cytomegalovirus infection.

The recognition by Gregg (1941) of the association between maternal rubella and congenital rubella defects led inevitably to the belief that other viruses might have a similar action, but in the event only one other, cytomegalovirus (CMV), has been found to be a significant cause of congenital defects. Other viruses listed in table I do from time to time

Proven	Not Proven
Rubella	Hepatitis A
Cytomegalovirus	Influenza
Herpes simplex	Mumps
Varicella-zoster	Coxsackie A or B
Variola-vaccinia	Echo viruses
Hepatitis B	
Poliomyelitis	

Table I *Effect on the fetus of virus infections in pregnancy*

infect the fetus and cause damage, but the incidence of fetal damage is small. Sever and White (1968) found that only 5·2% of 30000 pregnancies were complicated by a virus infection and a further 2% if serological tests were carried out. However, this does not take into account the fact that subclinical or latent viral infections may have a more deleterious effect on the fetus than we, at present, realize (Catalano and Sever, 1971). As far as the others, such as hepatitis A, influenza, mumps and the enteroviruses, are concerned, there is no convincing evidence that maternal infection leads to congenital defects, although they may indirectly lead to an in-

crease in fetal and infant mortality. Nevertheless this is an important area for investigation, principally because if a maternal infection can be identified as a cause of damage to the fetus or newborn, then the prospects of preventive measures being successful are better than in diseases of genetic or mixed genetic and environmental origin. For the purpose of this communication the term 'viral infections in pregnancy' will be taken to mean those infections acquired between conception and parturition and will include those congenital infections which, although acquired before birth, may not make themselves manifest until after birth.

If it is accepted that prevention is the ultimate objective in the study of virus infections in pregnancy, then it is necessary to obtain information on four related aspects: (1) the viral agents which are a significant cause of damage if infection occurs in pregnancy; (2) those factors which predispose to fetal damage; (3) the mode of infection and mechanisms of damage; and (4) details of the biological properties of the viruses responsible for fetal damage. In seeking to obtain this information it is helpful to study the way in which the evidence was obtained concerning the role of rubella virus as a cause of congenital defects. Gregg's original report (1941) recorded clinical observations of a repetitive pattern of defects, or clinical syndrome, associated retrospectively with an event in pregnancy. Epidemiological studies showed that the same clinical manifestations had been observed throughout Australia and many parts of the world. Twenty years later, with newly developed laboratory techniques available, it became possible to make a definitive and retrospective diagnosis of intrauterine rubella infection. The technique of virus isolation and tests for the persistence of rubella antibody, raised cord blood IgM levels and the presence of specific IgM antibody added much to our knowledge of congenital rubella. The evidence accumulated in this way has clearly established a cause and effect relationship between maternal rubella and certain congenital defects and the same applies to CMV infection. In attempting to establish a causal relationship between congenital defects and other virus infections, the

1 *Clinical*
    Each infection tends to produce a syndrome or repetitive pattern of clinical manifestations
2 *Epidemiological*
    The same manifestations should be observed with the same agent following maternal illness in different countries
3 *Virological*
    Persistence of the infective agent in fetal tissues and a chronic infective state after birth
4 *Immunological*
    Persistence of antibody in the child after the normal decline of maternal antibody; presence of antibody in the IgM fraction; raised levels of total IgM

Table II   *Criteria for establishing a causal relationship between a maternal infection and congenital defects or fetal damage*

criteria set out in table II should, as far as possible, be satisfied. It is not possible to satisfy them in all cases, but they serve as useful guidelines (Dudgeon, 1976).

Congenital Rubella

The original triad of symptoms—cataracts, heart disease and deafness—recognized by Gregg (1941) and Swan *et al* (1943) came to be known as the rubella syndrome. Following the rubella pandemics of 1963-1965 many additional clinical manifestations were observed as a direct consequence of intra-uterine rubella. Details of these are set out in table III, but 'new' manifestations are still being reported (Cooper, 1975), and it seems clear that the final picture of the impact of rubella virus infection on the fetus will be vastly different from the original restricted concept of the rubella syndrome. The way in which these clinical manifestations of congenital rubella may present are outlined in the figure.
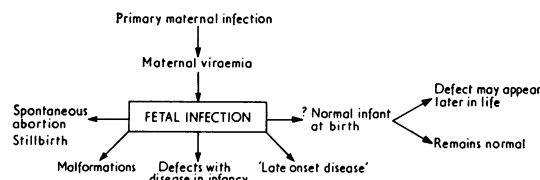

Fig.   *Consequences of intrauterine rubella infection.* (*After an illustration in* Brit. med. Bull., **32**, *1976*, 77).

An increase in the fetal mortality rate has been noted by several investigators (Manson *et al*, 1960; Siegel *et al*, 1966), but it is not an important feature. Premature delivery is infrequent whereas intrauterine growth retardation of an infant of normal gestational age is common. Malformations of the heart, eyes and hearing organs are frequently present, together with other defects such as neonatal purpura, hepatosplenomegaly, jaundice and hepatitis. The mortality rate in early infancy is high (Cooper, 1968).

General
    Intrauterine growth retardation; failure to thrive; retardation of postnatal growth
Eye Lesions
    Cataracts (80% bilateral); microphthalmos; pigmentary retinopathy; cloudy cornea; glaucoma; hypoplasia of iris, diminished reaction to atropine
Cardiovascular Lesions
    Persistent ductus arteriosus (PDA); PDA + pulmonary arterial lesions; pulmonary arterial lesions; (1) hypoplasia of artery, (2) supravalvular stenosis, (3) valvular stenosis, (4) peripheral branch stenosis; renal artery stenosis, ? cerebrovascular stenosis; aortic stenosis; ventricular septal defects; the tetralogy of Fallot; myocardial damage; neonatal myocarditis
Central Nervous System
    Microcephaly; fullness of fontanelle; raised protein and cells in cerebrospinal fluid (CSF); mental retardation; cerebral palsy; lethargy, hypotonia leading to irritability; unreactive, hypotonic infant; late onset of irritability and hypotonia; late onset of convulsions and meningitis; progressive panencephalitis
Hearing and Speech
    Sensorineural deafness; central auditory imperception; speech defects and deafness, with or without mental retardation; autism
Viscera
    Hepatomegaly; hepatitis and jaundice; splenomegaly
Bone
    Osteopathy
Blood
    Thrombocytopenia; purpura; anaemia
Lungs
    Interstitial pneumonitis
Skin
    Chronic rubelliform rash
Miscellaneous
    Persistent adenopathy; thymic hypoplasia; hypogammaglobulinaemia; recurrent or persistent diarrhoea; dermatoglyphic abnormalities; diabetes mellitus; ? growth hormone deficiency

Table III   *Clinical and pathological manifestations of congenital rubella*[1]

[1]Taken from Dudgeon, J. A. (1976) 'Infective causes of human malformations'. In: *Brit. med. Bull.*, **32**, no. 1, pp. 77-83. table I (p. 78).

Several features of congenital rubella, notably pneumonitis, rubelliform rashes, recurrent lung and gastrointestinal infections, may not develop until several months after birth; another well recognized feature of this so-called 'late-onset' disease is the type of sensorineural deafness which may not become evident until childhood. The same applies to a progressive form of encephalitis which can develop in the second decade of life (Townsend *et al*, 1975). A further important feature of congenital rubella is the fact that rubella in pregnancy, although frequently followed by fetal infection, does not always lead to fetal damage. It is now well established that the incidence of fetal infection in the first few weeks of pregnancy is very much higher than the incidence of congenital defects (Dudgeon, 1969). It can be seen from the figure that an infant apparently normal at birth may remain so or may develop signs of a defect after birth. The laboratory tests referred to in table II can provide useful information as to which of these infants have been infected as a result of exposure to maternal rubella and are, therefore, likely to be at greater risk. The risk to the fetus is determined by two factors: first, the immune status of the mother at the time of exposure to rubella, and secondly, the gestational age at which infection occurs. Primary maternal rubella in a susceptible woman without antibody at the time of exposure constitutes a risk to the fetus, whereas reinfection does not. Although there have been reports that reinfection has occasionally led to fetal damage (Weinstein *et al*, 1975), the evidence for this is slender, and the fact that there are no recorded and authentic cases of more than one case of congenital rubella in a family would appear to provide the strongest argument that reinfection is not a problem in the natural history of congenital rubella. The incidence of congenital rubella defects in liveborn infants summarized from several prospective studies between 1951 and 1964 is shown in table IV.

The detailed studies on congenital rubella patients over the past few years have also revealed important information on possible mechanisms of fetal damage. It seems likely that these are multifactorial rather than due to a single pathological process (Dudgeon, 1976). There is evidence of damage to placental and fetal blood vessels resulting in a sclerosing angiitis, of reduced mitotic activity and of cytolytic changes. Other defects can be attributed to persistence of virus and immunopathological mechanisms, but the vascular lesions may well be the most important of all.

Immunization against rubella with live attenuated vaccines, with the objective of preventing congenital rubella defects, was introduced in many countries in the early 1970s. Should these prove to be effective, the incidence of congenital rubella defects should decline during the next decade, and there is already some evidence from the United States (Cooper, 1975) that the incidence of rubella and congenital rubella is declining. The effectiveness of rubella vaccination programmes can only be determined by comprehensive and sustained surveillance programmes. The importance of these at the present time cannot be overemphasized.

Reference and Period Covered by the Study	*Gestational Age When Maternal Rubella Occurred*				
	First Month	*Second Month*	*Third Month*	*Fourth Month*	*Fifth Month and Over*
Lundström (1962)	29/87	41/163	18/218	6/142	2/621
Summary of 13 retrospective studies, 1946-51	(33·3)[1]	(25·2)	(8·3)	(4·2)	(0·3)
Swedish epidemic, July 1951- June 1952	13/113	18/150	15/186	3/204	2/468
	(11·5)	(12·0)	(8·1)	(1·5)	(0·4)
Liggins and Phillips (1963)	2/2	6/12	2/15	2/16	0/44
1959	(100)	(50·0)	(13·3)	(12·5)	(—)
Manson, Logan and Loy (1960)	7/45	12/61	10/77	3/72	5/288
1950-52[2]	(15·6)	(19·7)	(13·0)	(4·2)	(1·8)
Pitt (1961)	3/5	5/12	5/33	1/37	0/20
1956-59, interim report	(60·0)	(41·7)	(15·2)	(2·7)	(—)
Pitt and Keir (1965); Keir (1965)	3/5	4/12	11/32	2/35	0/19
1956-59, final reports	(60·0)	(33·3)	(34·4)	(5·7)	(—)
Siegel, Fuerst and Guinee (1971)	0/4	9/119	6/34	7/49	4/31
1957-63	(—)	(81·8)	(17·6)	(14·3)	(12·9)
1964	2/7	18/26	25/50	11/62	4/33
	(28·6)	(69·2)	(50·0)	(17·7)	(12·1)

Table IV *Incidence of congenital rubella defects in live-born infants*

[1]Percentages given in parentheses.
[2]In this study, one instance of a major defect, other than defects of the heart, eye and ear, and mental defects, was found as follows: erythroblastosis (at 0-4 weeks of pregnancy); oesophageal atresia, pyloric stenosis (at 5-8 weeks); duodenal atresia, pyloric stenosis (at 9-12 weeks); multiple gut defects (at 13-16 weeks); spina bifida, cleft palate, liver cyst, pyloric stenosis, imperforate anus (at 17 and more weeks).
Taken from Dudgeon, J. A. (1976) 'Infective causes of human malformations'. In: *Brit. med. Bull.*, 32, no. 1, 77-83, table II (p. 79).

Congenital Cytomegalovirus Infection

Cytomegalovirus is probably one of the most frequent viral infections of the human fetus and is a good example of how an inapparent, or latent, viral infection may have a deleterious effect upon the fetus. There are many points of similarity between congenital CMV and congenital rubella, both in respect of their clinical manifestations and natural history, but there are important differences which will be emphasized.

Cytomegalovirus is an extremely common virus infection of man but infection, unlike rubella, is nearly always asymptomatic. For this reason it is impossible, without serological tests, to determine the gestational age when the fetus becomes infected. Infection with CMV as determined by the acquisition of complement-fixing (CF) antibody appears to be acquired at two principal stages in life, whereas with rubella infection in most western countries takes place at a more regular rate. Stern (1975) has shown that in western countries CMV antibody develops fairly steadily from the age of 1 year to 15 years, by which stage 15 to 20% of individuals will have antibody. The next period of infection is between 15 and 30 years when about a third of the population will have acquired infection, so that primary infection is occurring with some degree of frequency during the main child-bearing period. In contrast, in crowded populations overseas, infection is acquired early in childhood leaving very few adults susceptible (Krech *et al*, 1971a). This pattern of events is probably related to the mode of spread of virus which requires close contact.

The consequences of intrauterine CMV infection follows the same pattern as shown in the figure for rubella, but again differences can be discerned. The relationship between inapparent maternal CMV and spontaneous abortion is uncertain. Various investigators have recovered CMV from aborted fetuses (Kriel *et al*, 1970) but these have not been confirmed by others (Boué and Loffredo, 1970; Marshall, 1972). The same wide spectrum of disease ranging from severe cytomegalic inclusion (CID)

disease, transient purpura, thrombocytopaenia, with or without neonatal hepatitis, to an asymptomatic infection, is encountered as in congenital rubella. Details of these are shown in table V but the main difference is that the severe multisystem disease, CID, is uncommon, whereas asymptomatic infection is very common. A further difference is that in congenital CMV damage to the central nervous system is more frequent, and, except for the rare occurrence of microgyria, structural malformations as seen in congenital rubella are extremely rare. In both cases, however, there is a substantial risk that a congenitally infected infant will later develop signs of mental retardation, with or without microcephaly, or deafness. The size of that risk is not at present known, but is an important question to answer when considering the need for preventive measures.

The pathogenesis of CMV differs in several important ways from that of rubella. In postnatally acquired infections, virus can be recovered from the nasopharynx, saliva, urine, cervical secretions, semen and breast milk (Stern, 1975). Primary infection in children and adults is usually followed by transient excretion from the throat and urine, but infection may remain for longer periods in the uterine cervix. Cytomegalovirus behaves like other DNA viruses of the herpesvirus group in that virus is not completely eliminated following primary infection, but remains latent and, therefore, capable of reactivation. The two situations in which reactivation may occur are pregnancy and in patients on immunosuppressive therapy (Stern and Tucker, 1973). The virus excretion rate increases in seropositive women during pregnancy, being higher in the third trimester than in the first and second (Montgomery *et al*, 1972). Studies by Stagno *et al* (1975) indicate that early pregnancy has a suppressive effect on viral excretion. The overall recovery rate of virus from the cervix and urine of pregnant and non-pregnant females was similar, being 9·4% and 9·5% respectively. However, in the pregnant group the recovery rate in the first trimester was 1·6% compared with 11·3% in the third. Virus can be recovered from the same sources as before, so that

Generalized Cytomegalic Inclusion Disease (CID)	Localized Disease	Asymptomatic Infection
Low birth weight	Purpura	
Hepatosplenomegaly	Hepatitis	
Hepatitis: jaundice		
Encephalitis		
Irritability: hypotonia		
Hydrocephalus		
Microcephaly		
Chorioretinitis		
Cerebral calcification		

Table V   *Consequences of congenital CMV infection*

at parturition the infant may become infected by cervical secretions or from virus-infected breast milk. Infants infected in this way may excrete virus for prolonged periods. There seems little doubt that primary infection associated with maternal viraemia is the main source of congenital infections with defects, but to what extent perinatal and early neonatal infections can lead to infection and damage to the infant brain is not known.

Hanshaw *et al* (1973) have estimated that between 0·4% and 1% of live-born infants are congenitally infected with CMV. Stern (1975) found that approximately 1-2% of pregnant women in London developed a primary CMV infection and that 50% of the newborns were infected and excreting virus at birth. In round numbers this means that as far as the UK is concerned, between 4000 and 10 000 infected infants will be born each year and that of these, approximately 10% may be damaged. Although the rate of infection increases throughout pregnancy, the risk to the fetus does not. Monif *et al* (1972) found that mothers, who became infected in the second trimester, gave birth to infants with symptoms, whereas those infected during the third trimester had normal or uninfected infants. Serological tests carried out by Hanshaw *et al* (1973) indicate that children born to mothers who had CMV infection in pregnancy, but who had antibody at the time, which was not the result of a primary infection, were not infected. This strongly suggests that reactivation is not an important problem in the causation of defects; nevertheless there have been reports of congenital CMV in successive pregnancies (Embil *et al*, 1970; Krech *et al*, 1971b; Stagno *et al*, 1973), but it is not clear whether the second infected children are damaged. In one case reported by Stagno *et al* (1973) the second infected child has shown no evidence of physical or motor impairment at 9 months of age. Second infections could be related to reinfection with a different strain of virus, but as strains of CMV are so closely related this explanation seems improbable (Stagno *et al*, 1973).

Less is known about the pathology of congenital CMV than about congenital rubella, but necrotic and inflammatory changes appear to predominate in CMV. There is also evidence from the work of Hayes and Gibas (1971) that primary CMV infection may be halted at the level of the placenta with the result that the fetus is spared.

Congenital CMV presents a more important problem from the point of view of management and prevention than does rubella. More children are damaged by this virus; the damage is not amenable to corrective surgery as in the case of some of the defects caused by rubella virus. There is no simple way of telling when a primary CMV infection has occur-

red in pregnancy. Finally, prevention by immunization, certainly with a live vaccine, presents a number of imponderable problems (Dudgeon, 1973). These are associated with latency of infection, and the possibility of oncogenicity with a DNA virus, and, although the risks may be small or even non-existent, there is no way known at present as how to answer them.

Herpes Simplex Virus

Herpes simplex virus (HSV) infections occur with even greater frequency than CMV infections, and again the majority are asymptomatic. Infection of the fetus and newborn can occur at two stages of pregnancy. The most frequent is late in pregnancy, or actually at birth, when the fetus may be infected as the result of an ascending cervical-amniotic infection from genital herpes of the mother or by being infected on passage through the birth canal. Neonatal infection is being recognized with increasing frequency due to a greater awareness of the frequency of genital herpes in women and improved methods of laboratory diagnosis. Nahmias *et al* (1975) have found that 88% of such infections are due to HSV type 2 strains; three-quarters of the isolates from 120 newborns were type 2 strains. However, no significant difference in the clinical manifestations have been observed between HSV-2 and HSV-1 strains. Both can cause disease ranging from severe disseminated infections involving the skin, viscera and brain to mild infection of the skin or oral mucosa, but subclinical infection in the newborn is very infrequent. Maternal genital herpes is also associated with increased abortion and premature delivery (Nahmias *et al*, 1971).

Transplacental infection may also occur leading to fetal infection earlier in pregnancy. Schaffer (1965) described a case with signs of microcephaly, periventricular intracranial calcifications, microphthalmia and cutaneous lesions from which HSV was isolated. The child was sick at birth and was probably infected early in fetal life. A case reported by South *et al* (1969), born at 33 weeks' gestation, had marked microcephaly, microophthalmia, intracranial calcification and retinal dysplasia. The mother had a history of genital herpes before and during the pregnancy. Montgomery *et al* (1973) described a further child with chorioretinitis and retardation, patent ductus arteriosus and short digits in whom skin lesions were present at birth and which persisted as scars. The mother had had a febrile illness at six weeks of gestation but no evidence of genital herpes. Herpes simplex virus -2 was recovered from the skin lesions at the age of 14 months. Congenital infection was presumed. Two additional cases with neuro-

logical damage have been seen recently (Hanshaw, 1975).

Although so few cases have been reported, this may well be due to a lack of recognition of signs and symptoms which may be associated with intrauterine HSV infection and the absence of laboratory facilities to substantiate the diagnosis.

Varicella-zoster Infections

The effect of varicella-zoster (V-Z) infections on the fetus and newborn is similar in many respects to HSV infection. Maternal varicella acquired in the last 10 days of pregnancy can lead to infection, presenting at birth or early in the neonatal period (Gershon, 1975). The severity of the infection varies considerably; many infants escape infection altogether, others have a mild vesicular eruption, whilst a few develop a severe disseminated infection. The severity of the infant's illness appears to be related to the time of onset rather than to the severity of the maternal disease. In a series of 50 cases reviewed by Gershon (1975) it was found that where the mother's illness was contracted five days or more before delivery (and the onset of the baby's illness within four days of birth) all 27 infants survived; whereas if maternal varicella developed within four days of birth (and the baby's illness five to 10 days afterwards), seven out of 23 infants died (mortality rate 14%). Overall, the mortality rate of neonatal varicella is from 14% to 31%.

Varicella-zoster infection contracted early in pregnancy may rarely lead to congenital defects. Laforet and Lynch (1947) first drew attention to a possible relationship between varicella in pregnancy and a series of defects characterized by paralysis, muscular atrophy of a limb, cutaneous scars, rudimentary digits, convulsions and cortical atrophy. Since then seven other cases with essentially similar defects have been seen in different parts of the world (see reviews by Gershon 1975; Dudgeon, 1976). A summary of the main clinical findings is shown in table VI.

Defect	No of Infants Affected
Low birth weight	5/8
Cutaneous scars	8/8
Hypoplasia of a limb	6/8
Rudimentary digits	4/8
Paralysis with muscular atrophy of a limb	5/8
Convulsions and/or phychomotor retardation	4/8
Chorioretinitis	3/8
Cataracts and/or other eye defects	2/8
Cortical atrophy	3/8
Death	5/8

Table VI *Summary of clinical details in eight cases of congenital varicella*

Variola-vaccinia Infections

Fetal infection with variola-vaccinia virus follows the same pattern as observed with HSV and V-Z virus infections. The fetal mortality rate is increased after maternal smallpox (Lynch, 1932) but the incidence is not known with any accuracy as records from countries where the disease is endemic are not available. Alastrim, or variola minor, can also cause fetal death. Two cases have been reported in detail by Garcia (1963) of macerated fetuses following alastrim at the fourth and fifth month of pregnancy in which diffuse necrotic lesions were found in the placentae and fetal viscera.

Smallpox contracted close to term can cause neonatal infection very similar to that observed in maternal varicella. Marsden and Greenfield (1934) observed 33 women who contracted smallpox during the latter stages of pregnancy. This was almost certainly due to alastrim, or variola minor, as there were only a few deaths out of 13 000 patients admitted to the smallpox hospitals in London at the time (1929-1934). The 33 pregnant women gave birth to 36 infants (three twin pregnancies); of these 22 developed variola and 14 escaped. Those infants who developed infection were born during the prodromal illness of the mother or within seven days of onset of maternal rash. The infants who escaped infection were either born before the mother's illness or at least a week afterwards.

Vaccinia virus can also cause fetal infection. Approximately 20 cases have been recorded in the literature (Levine *et al*, 1974), nearly all of which followed primary vaccination in pregnancy or revaccination after a long interval. Only three of the liveborn infants survived and one of the features of these was the presence of large scars on the infant's skin (Harley and Gillespie, 1972). This was also a feature of a case seen by Bray (1975) following primary vaccination at the 24th week of pregnancy. The fatal cases have usually been associated with macerated fetuses and diffuse necrotic lesions on the skin and in the viscera (MacDonald and MacArthur, 1953; Tucker and Sibson, 1962).

Although the risk of fetal damage is small, vaccination is contraindicated in pregnancy unless there has been a definite contact with a known case of smallpox. Vaccination against smallpox should normally be carried out as an elective procedure.

Perinatal Hepatitis B

The recent development of sensitive methods for the detection of hepatitis B antigens and antibody has enabled investigators to study the effect of maternal hepatitis B infection on the fetus and newborn

(Zuckerman, 1975). Studies by Schweitzer *et al* (1973a) have identified two main types of effect. Thirteen babies born of 27 mothers who had developed overt disease acquired antigenaemia without clinical illness which persisted for prolonged periods. There was also prolonged elevation of the transaminase levels, and liver biopsies in these infants revealed unresolved hepatitis. In contrast only one infant born of an asymptomatic carrier-mother became antigen positive. Transmission of hepatitis B occurs more frequently when infection occurs in the third trimester or in the immediate postpartum period (76%) and in only 10% where hepatitis occurred during the first six months of pregnancy (Schweitzer *et al*, 1973b). Acute hepatitis developed in two infants but the antigenaemia was only transient.

Poliomyelitis

Poliomyelitis in the newborn following maternal poliomyelitis in late pregnancy was a very rare occurrence before immunization against poliomyelitis was introduced. It is now a matter of academic interest. Baskin *et al* (1950) and Johns (1948) reported three cases of severe paralysis developing with the first seven days of life; two of the three infants died and the third was severely paralyzed. Other cases have been reviewed by Pugh and Dudgeon (1954) and by Katz (1975).

Other Virus Infections

The evidence that other virus infections can cause fetal infection or fetal damage is unconvincing (see review by Dudgeon, 1976) but the possibility that subclinical infection can cause damage must not be overlooked. Reports that maternal influenza can lead to defects of the central nervous system have been repeatedly made in the past 20 years, but if there is a cause-and-effect relationship it only occurs spasmodically. Godber (1972) has suggested that the increase in the neonatal mortality rate in the UK in 1950-51 and in 1969-70 may have been related to an influenza epidemic which occurred a few months previously. The matter is being further studied.

Mumps has been incriminated as a cause of primary endocardial fibroelastosis (St Geme *et al*, 1966) but with no convincing corroborative evidence (Katz, 1975).

The enteroviruses other than poliovirus have also been studied in some detail as a cause of fetal infection, but although they may effect the newborn and cause severe disease, there is no clear evidence of fetal infection.

A review of the effect of other virus infections on the fetus and newborn has recently been made by Katz (1975).

Summary

Although rubella is the only virus which can be regarded in the strict sense of the term a teratogen, there is no convincing evidence that other viruses can cause fetal damage of varying severity. The risk to the fetus appears to depend on the nature of the infectious agent, the maternal immune status and the gestational age when infection takes place. The possibility that subclinical maternal infections may cause damage must not be overlooked. As some of the viruses referred to can cause damage after the period of organogenesis, the use of the term 'teratogenic effect' in relation to viral infections is considered to be inappropriate.

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