Regular Review

Virus infections (other than rubella) during pregnancy

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When a virus infection occurs in pregnancy[1] concern about the effects on the fetus[2] inevitably parallels attention to the health of the mother. In fact, the fetus is seldom infected, but when it is the results may be catastrophic. Infection may also occur at delivery, from the genital canal or from the blood of the mother if she is a carrier of a virus. The obstetric attendants may be at risk at delivery—as also may the father if he is present.

Virus infections may not follow the usual course during pregnancy, when cellular immunity seems to be depressed[3] and corticosteroid concentrations to be raised. The effects of infections with smallpox, poliomyelitis,[4] varicella,[5] and influenza[6] may all be worse in pregnancy. Early reports of hepatitis during pregnancy did not differentiate between hepatitis A and hepatitis B, and the nutritional state of the patient is another important factor. Certainly in malnourished patients the mortality from hepatitis appears to be higher but this is not necessarily true in the healthy gravid woman.[7]

By far the most common outcome of viral infections in the mother is that the fetus is not infected, and that pregnancy runs its normal course, with delivery of a healthy, full-term infant. Wider appreciation of this good prognosis would save many unnecessary terminations of pregnancy and allay much unjustified fear on the part of women continuing pregnancy after a virus infection. If, however, the fetus is infected the abnormal consequences may be early death, leading to abortion; death later in pregnancy, followed by stillbirth; defective organogenesis and the survival and birth of a fetus with one or more congenital malformations; retardation of growth, with birth of an apparently normal infant of low birth weight; or, finally, infection of the fetus just before delivery (or of the infant just after delivery) giving a congenital or neonatal infection.

After rubella the best attested example of a virus which affects the unborn baby is cytomegalovirus.[2 8] Indeed cytomegalovirus infections may claim to be of greater numerical importance than rubella. For most other viruses the information is at best scanty and at worst merely anecdotal. Not only are the reports for any one virus much fewer but in any individual case there is always a possibility of an unsuspected contact with rubella at the crucial stage of pregnancy.

Cytomegalovirus—Our knowledge of congenital infections has recently been fully reviewed.[2] In England and Wales, where the virus is widespread, some 400 babies a year are born mentally retarded because of primary infection of the mother in pregnancy by this virus.[9] Furthermore, the full syndrome of infection with cytomegalovirus, with severe brain damage, is only a part of the total toll. Many more babies are symptomless excreters of the virus, and some of these also have a low birth weight and eventually show varying degrees of retardation. In contrast with rubella, diagnosis is rarely straightforward, since the illness is almost always subclinical. Occasionally there is an illness resembling glandular fever but with negative results to Paul-Bunnell testing, but such cases are few. Most often diagnosis is feasible only by monitoring throughout pregnancy all women with no antibodies to the virus—preferably with determination of IgM as well as IgG antibodies. Serological diagnosis is less easy because of the need to use the relatively insensitive complement-fixation reaction. The proportion of women who have a cervical infection with cytomegalovirus at some time during pregnancy varies between 3% and 28%.[10 11]

In women with antibodies at the outset of pregnancy secondary infection, or reactivation of latent infection, is generally assumed to be innocuous to the fetus, and this is probably true. Unfortunately—and again in contrast with rubella—the proportion of cytomegalovirus-negative (and hence susceptible) women is rising as a result of improved hygiene.[12 13]

What, then, can be done to protect cytomegalovirus-negative mothers from infection during pregnancy? Far too few patients are screened for antibodies at antenatal clinics. This could, and should, become a routine test. Those found to be seronegative (a third to one-half of all pregnant women in Britain) should be watched for any febrile illnesses or mononucleosis-like syndromes. Serological monitoring on the scale required is not a practical proposition, at least at present. Any women who need blood transfusion during pregnancy should be given blood free of cytomegalovirus antibodies (and hence presumed free of the virus). What if an infection is detected? The difficulty is to find out whether the fetus as well as the mother has been infected. Culture of the virus from the cervix or from the urine does not necessarily imply fetal infection, and hence culture of amniotic fluid has been advocated, but amniocentesis is not a procedure to be undertaken lightly. There is no accepted method for assessing the risk to the fetus, even when symptomatic, clinically overt, infection of the mother has been established. Hence clear guidance cannot be given about termination of pregnancy.

Whether or not there is a danger of transmission of cytomegalovirus from an infant to a woman doctor or nurse has to be established, but Hanshaw and Dudgeon[2] suggest that such workers should be tested for antibodies. Those who are negative should not care for infants with overt cytomegalovirus disease, and, in addition, known virus-excreting infants should be nursed in isolation. Studies of patients

Virus infections of the mother, fetus, neonate, spouse, obstetrician, and paediatrician

Virus infections of the mother, fetus, neonate, spouse, obstetrician, and paediatrician	Rubella	Cytomegalovirus	Herpes simplex	Varicella-zoster	Genital warts	Vaccinia	Smallpox	Hepatitis B	Hepatitis A	Poliovirus	Coxsackie B	Influenza	Mumps	Measles	Marburg virus
Mother															
Acute infection in pregnancy (+ + worse in pregnancy)	+	+	+	+ +	+	+*	+ +	+†	+†	+ +	+	+ +	+	+‡	+§
Relation to carcinoma of cervix uteri	−	−	?	−	?	−	−	−	−	−	−	−	−	−	−
Fetus/neonate															
Abortion	+	?	?	?	−	+	+	?	+	+	?	+	+	+	?
Stillbirth	+	+	−	?	−	+	+	?	?	+	?	+	+	+	?
Malformation	+	+	+	+	−	?	−	−	−	−	−	?	?	?	?
Low birth weight	+	+	+	+	−	+	?	−	+	+	−	?	−	−	?
Congenital infection	+	+	+	+	?	+	+	+	−	+	+	−	−	?	?
Spouse															
Sexually transmitted disease	−	?	+	−	+	−	−	+	−	−	−	−	−	−	+
Obstetrician/paediatrician															
Mother as source of infection	+	?	+	+	+	+	+	+	+	+	+	+	+	+	+§
Fetus/neonate as source of infection	+	?	+	+	−	+	+	+	+	+	+	−	−	−	−

*Smallpox vaccination now contraindicated in general.
†Viral hepatitis worse in pregnancy in malnourished patients.
‡Measles infection at child-bearing age rare.
§Not recorded in pregnancy.

excreting cytomegalovirus in the urine or throat have shown that virus may be shed for many months. Long term the problems of these infections in pregnancy will disappear only when there is a satisfactory vaccine. Fears about the oncogenicity of such a vaccine have been given more weight than potential benefits but one is urgently needed.[9 14]

Varicella—Chickenpox is uncommon in pregnancy, since most women have had it before they reach childbearing age. In pregnancy varicella may be more severe than in the non-pregnant woman. Until recently it was thought not to cause congenital defects, but eight cases have now been reported[15 16] of the congenital varicella syndrome: cerebral cortical atrophy and cerebellar hypoplasia, manifested by microcephaly, convulsions, and mental retardation. In addition, there may be hypoplasia of a limb or limbs, with rudimentary digits, and pigmented scars of healed lesions on the limbs. This is a catastrophic but probably very rare effect. Nevertheless, if a mother has been in contact with varicella and gives no history of the illness, a dose of zoster immune globulin may be given within three days of exposure to protect the infant during the viraemic phase. At the other end of pregnancy there is also a risk to the fetus, and the administration of zoster immune globulin is also justified to infants of mothers who contract varicella within five days of delivery or in the first few days after birth.

Zoster is caused by the same virus as varicella. A case of zoster at 37 weeks of pregnancy has recently been described with subsequent delivery of a normal infant.[17] Zoster in pregnancy is rare, with only 13 recorded cases. Two of the fetuses had a picture resembling the congenital varicella syndrome, and a third (also abnormal) had been exposed to rubella at 2 months. The other 10 were normal. Contact with zoster should be managed in the same way as contact with varicella. Contact with this virus should not be viewed as a ground for termination of pregnancy.

Herpesvirus hominis (herpes simplex)—Infection of the fetus via the placenta may occur from infection of the gravid woman with herpesvirus, but it probably requires the combination of pregnancy with a primary infection and viraemia.[2 18] Either extragenital or genital herpes may lead to abortion, but the risk is probably higher with genital infections. Congenital malformation is unusual, but serious,[19] with the central nervous system as the main target system. Lesions include microcephaly, chorioretinitis, and microophthalmia. These abnormalities have been reproduced in animals given infection with *Herpesvirus hominis*.[20] The infant may be born prematurely with fulminant and usually fatal general disseminated herpes affecting the skin, brain, lung, liver, and spleen. Caesarean section should be considered to protect the infant when a woman has *Herpesvirus hominis* present in the genital tract before delivery.[18] Non-specific immunoglobulin has not been shown to be of any value. With constant improvements in the drugs available the place of chemotherapy has to be defined in the treatment of neonates with generalised herpes. Infection from the maternal genital tract is more frequent than transplacental infection and is usually, though not exclusively, caused by type 2 herpesvirus.

Smallpox and vaccinia—Since the presumed recent eradication of smallpox and the consequent progressive abandonment of antismallpox vaccination these two viruses have become anachronisms. Nevertheless, vaccination against smallpox is not yet extinct, and conceivably smallpox or a smallpox-like virus could reappear. Both viruses affect the fetus and neonate.[2] Smallpox causes increased fetal death in the first half of pregnancy and premature delivery in the second. The effects of vaccinia administered in pregnancy were studied in Glasgow by MacArthur,[21] who found a much higher incidence of fetal death, especially in women vaccinated in the second and third months of pregnancy. Vaccination is contraindicated at all stages of pregnancy, but if inadvertently performed in early pregnancy is not a ground for termination. Probably one of the last cases of vaccination[22] in pregnancy which will ever occur was reported last year. The patient was vaccinated at eight weeks. At 24 weeks she was delivered of an infant weighing 500 g which survived for one hour. Vaccinia virus was isolated from the lung and from multiple skin lesions. Almost all reported cases of fetal vaccinia have followed primary vaccination. In the rare event of a woman being at risk from variola, vaccinia and antivaccinial immunoglobulin may be given simultaneously.[23]

Papovaviruses—The recently discovered papovaviruses[24] have been detected in the vaginal secretions of pregnant

women.[25] It appears that most women (perhaps 90%) have antibody to the BK virus, which is also commonly isolated from patients with renal transplants. Nevertheless, there is no evidence that BK infection can cause fetal malformation or seriously harmful congenital infection. A woman from whose urogenital tract the second papovavirus, JC, was isolated at 36 weeks of pregnancy was delivered of an infant normal except for a high serum bilirubin concentration.[25] No positive evidence has come to light of serious harm caused to the fetus by these viruses in spite of the fact that they are present in the urine of about 5% of pregnant women.

Hepatitis B—Hepatitis B is a DNA virus whose presence can be recognised by testing for hepatitis B antigen.[26] The pregnant woman may be a symptomless carrier of the virus or may have an acute attack. Acute clinical hepatitis B in pregnancy is rare,[7 27] but, because of heavy viraemia, may cause neonatal infection and be a hazard to the obstetric attendants. Viraemia precedes clinical illness, so that infections in the second half of pregnancy, and in the first few weeks of the puerperium, are a hazard to the infant, and an indication for giving specific antihepatitis B immunoglobulin after birth.

The carrier state is much more common in pregnancy than is clinical infection, but, paradoxically, it is less dangerous to the fetus.[28] About one-third of carriers have the hepatitis B "e" antigen (HBeAg) as well as the surface antigen (HBsAg), and these are more likely to transmit the virus to their offspring at, or soon after, birth. Mothers of the Chinese race are more likely to transmit than others.[29] There is no evidence that hepatitis B or hepatitis A (which is an RNA virus, quite distinct from hepatitis B) causes congenital defects, and infection during pregnancy is no ground for termination. In the mother acute hepatitis during pregnancy is more hazardous than at other times, but there is great local variation throughout the world, and nutrition may well play a large part in the fate of the patients. One interesting but unexplained effect is an increased sex ratio of boys to girls in children born to hepatitis B carriers.[30]

Poliomyelitis—Poliomyelitis has been reported to be worse in the pregnant woman.[4] Most women who have poliomyelitis in pregnancy will be delivered of a healthy, full-term infant. There is no evidence that the virus causes congenital defects. Abortion and stillbirth may occur, but it is uncertain whether this is due to viral infection of the fetus or to the general effects of the maternal febrile illness. Nevertheless, the virus can cross the placenta. Neonatal poliomyelitis has about a 25% mortality.[31]

Other enteroviruses—Other enteroviruses can cause serious neonatal disease,[32] particularly the Coxsackie B viruses, but there is no reliable evidence that they cause congenital defects. Even neonatal infection may be inconspicuous, subclinical,[33] or an unsuspected cause of perinatal death.[34]

Influenza, measles, and mumps—These viruses are associated with an increased fetal mortality, but there is little evidence that this is more than a result of the serious febrile illness in the mother. There are no grounds for supposing that they cause congenital defects by direct infection of the fetus.

In summary, then, the precise danger to the fetus of intrauterine or perinatal infection varies with the virus and with the mother's immune state. Specific immune globulins can be used prophylactically in some circumstances, and antiviral chemotherapy may be applicable. The precise nature of the virus needs to be known if treatment is to be specific and rational. Though some viruses, and especially rubella and cytomegalovirus, can have serious effects on the fetus, most other viruses affect the fetus exceptionally or not at all.

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