H. VIRAL INFECTIONS

76. INTRODUCTION TO VIRAL INFECTIONS IN PREGNANCY

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CLASSIFICATION

Attempts have been made to classify viruses in the same manner that has been used to classify bacteria. In recent times this has succeeded to a limited extent. However, it is not possible to assign a species classification in most instances, nor has isolation of all viruses been accomplished, so that even a genus category is tentative for many viruses. Be that as it may, great strides have been made to classify more than 400 viruses known to infect man. In general, viruses can be defined as follows: (1) they all have a nucleic acid or genome surrounded by a protein shell, and (2) viruses can multiply only within a living cell since they have no synthetic or energy-producing systems of their own.

The major criteria for assigning any virus to a particular category or family are the morphologic, genetic, physical, and chemical properties of the virus particle or virion. Various combinations of these criteria will produce the same categorical breakdown of viruses; therefore, it is not yet clear whether all of these criteria are needed or which system is better than another. For example, a system of classification using just the structure and size of the viral genome will result in a listing that is the same as a classification based simply on electron microscopic morphology.

The major families of viruses that infect man are listed in Table 76-1 and are divided into groups by the type of nucleic acid found in the nucleocapsid. Many other morphologic factors could be listed in this table, such as whether the nucleic acid is single or double stranded, whether an envelope is present, or what the molecular weight is. These details are more appropriate for a text on basic virology and are not necessary for this discussion.¹⁻³

PATHOGENESIS

In order for any virus to produce an effect or cause disease it must gain entrance to the cell. On a cellular level all viruses produce a cytopathic effect that may be easily recognized or may be very subtle and measured only with sophisticated biochemical or immunologic means. The first step, therefore, requires the virus to gain access to

the cell, a process referred to as adsorption. This occurs because of the presence of specific receptors on the cell surface. There are usually a large number of viral receptors on a cell so that a large number of viral particles may be adsorbed. The next steps necessary for the virus particle to reproduce within the cell and achieve the characteristic cytopathology are penetration and uncoating. The first of these two steps is obvious, as the virus particle can be seen entering the cytoplasm. The uncoating of the viral genome is a process by which the protective protein coat is stripped away from the nucleic acid so that the genome

TABLE 76-1. Major Families of Viruses Infecting Man

Family	Size (nm)	Examples of viruses in this family
DNA viruses		
Adenoviridae	70-90	31 different serotypes
Herpesviridae	150-200	Simplex, varicella, CMV, EB
Papovaviridae	45-55	Papilloma, polyoma
Parvoviridae	18-26	Adeno-associated viruses
Poxviridae	200-300	Variola, molluscum
Unknown	40-50	Hepatitis B
RNA viruses		
Arenaviridae	80-130	LCM, Tacaribe, Lassa
Bunyaviridae	100	Arbor, California encephalitis
Coronaviridae	80-130	Infectious bronchitis virus
Orthomyxoviridae	80-120	Influenza viruses
Paramyxoviridae	150-300	Parainfluenza, mumps, measles
Picornaviridae	20-30	ECHO, polio, Coxsackie, rhino
Reoviridae	60-80	Respiratory-enteric-orphan
Retroviridae	150	Leukemia viruses
Rhabdoviridae	75-80	Rabies, Marburg, Ebola fever
Togaviridae	40-60	Rubella, EEE, yellow fever dengue, St. Louis encephalitis
Unknown	25-30	Hepatitis A

becomes available for the next or synthetic step in viral reproduction.

The synthetic phase of viral-cell interaction utilizes the cell's own machinery to accomplish genome replication, synthesis of viral proteins, and completion of progeny virus. These processes take place either in the cell nucleus or the cytoplasm depending on the particular family of viruses. In addition, part of the synthetic phase may occur in the nucleus and part in the cytoplasm; however, viral protein is synthesized in the cellular cytoplasm since that is the location of the ribosomes and messenger and transfer RNA, which the virus must use.

The last step in the process of viral multiplication is release of viral progeny. In some viruses this process may result in the coating of the nucleocapsid by host cell membrane protein. However, most viruses are simply released from the cell. Both coated and uncoated viruses are released from the cell as the cell dies. This is known as a lytic effect; however, why lytic viruses destroy their cells is not clear. The most obvious effect of cell lysis is the cytopathic effect that can be observed in cell culture or in individual cells by microscopy. Once the cell dies, it releases large amounts of virus (unless the virus buds from the cell membrane, in which case the virus remains attached to the cellular debris from the dying cell). This train of events probably occurs in the intact host (as contrasted to a cell culture system) with the addition of the possibility that the phagocytosis of lysed cells causes dissemination of the virus throughout the host.

Lytic viruses are not the only ones that produce a pathogenic effect in man. Some viruses establish a stable relationship with permissive cells such that cell growth and viral multiplication occur together. This results in a chronic or persistent viral infection. The best example of this is the in utero infection of the fetus with rubella, which continues to be shed without causing cell death for many months after delivery. Other possible examples of persistent virus infection with pathologic effects are subacute sclerosing panencephalitis by a virus similar to or identical to measles virus (rubeola) and progressive multifocal leukoencephalopathy by a papovavirus.

Another form of persistent virus infection without cell death is the latent phase of several viruses that cause recurrent lytic infection in some other cell. Examples of these are the viruses in the Herpesviridae family, herpes simplex, varicella-zoster, and cytomegalovirus.

Once the cellular events described above occur, the resultant pathology in the host is attributable to the usual changes that are seen with any infectious disease, i.e., inflammation, tissue destruction, and immunologically mediated cellular and tissue destruction.

The pathogenesis of viral infection in pregnancy, for the most part, is no different from that in the nonpregnant state. This is true when one refers to the viral-cell interaction in general; however, if one looks at a few specific viral infections, there are some anecdotal and retrospective data that suggest that that virus is more pathogenic during pregnancy. For example, the pandemic of influenza in 1918 and subsequent epidemics have led some investigators to conclude that the attack rate was higher and the morbidity and mortality among adult women were worse during pregnancy. Another example is varicella-zoster infection. Some authors have sug-

gested that the pregnant adult has a greater tendency to develop varicella pneumonia with its attendant morbidity and mortality than the nonpregnant female. Unfortunately, the prospective data on these two virus infections in pregnancy are limited and do not answer the question, "Are influenza and varicella infections worse in pregnancy?" Suffice it to say at this point that they may be, but there are not good data to support this answer.⁴

Poliomyelitis is perhaps a better example of a virus causing a more serious infection during pregnancy. Again, the data are retrospective and not confirmed by any laboratory or clinical data. However, a patient-controlled study from 1955 suggested that pregnant women are more susceptible to the development of poliomyelitis and have a higher mortality rate.⁵

What the pathogenic mechanisms may be in pregnancy that could account for some virus infections being worse in pregnancy is a matter of speculation. There are, however, some interesting experimental models that offer some clues. One experiment showed that mice vaccinated against St. Louis encephalitis virus during pregnancy did not develop antibodies until 7 weeks postpartum.⁶ Several experiments have demonstrated that the hormones of pregnancy will affect the growth of some viruses both positively and negatively.⁷ At least two changes—altered immune response and increased growth related to the hormones of pregnancy—may be examples of why a virus may be more virulent in pregnancy. Yet the vast majority of viruses seem to affect pregnant women in the same manner as nonpregnant women. These points are discussed more fully with each virus described in the next several chapters.

DIAGNOSIS

Virus infections, like bacterial infections, are diagnosed most appropriately by isolating the organism from the site of infection.⁸ However, this is not always possible: either the virus is producing a systemic infection so that no one site is available (e.g., rubella) or the virus is not a lytic one, so that no virus is available outside the cell (e.g., some of the encephalitis viruses), or the virus is a latent one, so that there is no virus available anywhere (only its genetic material is present in some cells; e.g., the herpesviruses), or techniques are not yet available for isolating that particular virus (e.g., human papillomaviruses). The term "isolation" when applied to viruses refers to the changes that one can observe in a host cell (cytopathic effect) or whole organism. One does not usually "see" the virus because of its size. However, one can see the effect of the virus in an appropriate cell culture system or the effect of the virus on an animal.

The clinical virology laboratory can provide the standard "systems" for isolation of many viruses. The cell culture systems include primary monkey kidney cells, primary human embryonic kidney cells, and human diploid and human heteroploid cells. The usual animal systems include suckling mice and embryonated chick eggs. Beyond these there are a number of other cell and animal models available to which only specialized laboratories have access. Certain viruses (EB, coronaviruses, and some of those viruses associated with chronic degener-

ative brain diseases) can be isolated only in specialized laboratories. Because of the risk of epidemics and the potential economic loss, viruses such as that for hoof-and-mouth disease are restricted to certain laboratories.

Unlike most bacterial infections, viral infections also can be diagnosed by serologic techniques. Demonstration of a greater than fourfold rise in an antibody titer to a particular virus is satisfactory evidence of a recent viral infection. The type of antibody to be measured (neutralizing, complement-fixing, hemagglutinating, fluorescing, etc.) varies with the particular virus under investigation. In addition to detecting the antibody to a virus, one may be able to detect the antigen of a virus present in the tissues of the individual under investigation. This has been done with immunofluorescence, immunoperoxidase assays, and counterimmunoelectrophoresis.

Finally, the presence of a virus may be detected by observing it, as is done with most bacteria. This is done infrequently in the clinical setting because of the requirement for electron microscopy. However, for such organisms as papillomavirus or human wart virus, this is the only means available.

Given the large number of viruses, the multitude of isolation techniques, and the antigen and antibody detection techniques available, it is in the clinician's best interest to work closely with the clinical virologist in order to determine the most efficient and reliable means to diagnose a suspected viral infection.

CONTROL

There are numerous ways to control the spread of viral infections. These vary from specific antiviral therapy to removal of the vectors of virus transmission to active immunization of individuals. To some degree all of these are used today.

Perhaps the oldest of the standard control methods for viral infection is the attention that is given to the vectors of transmission. This idea is taken directly from those methods used for controlling certain bacterial diseases such as plague and brucellosis. Removing the mosquito hosts for the encephalitis viruses reduces the incidence of infection. Removing the rabid animal—or avoiding animals known to harbor rabies—reduces the chance of this virus infection.

The newest control measure for viral infection is the use of antiviral therapy—analogue to antibiotics. This era began in the middle 1960s with the development of amantadine hydrochloride, which works against influenza virus by inhibiting its undercoating. It is most effective when used prophylactically, and it has no beneficial effects against any other human virus infection.

Another class of antiviral is that which inhibits viral replication by interfering with nucleic acid production or its incorporation into nucleotides. *Idoxuridine* (Stoxil[®], *Herplex*[®]) was the first of these compounds and was used for herpesvirus infections of the eye, for which it is still used. *Vidarabine* (ARA-A) is used for the same indication. In addition, it is used for the systemic treatment of disseminated herpesvirus infections. Both of these compounds are useful in vitro against DNA-containing viruses only. The former is incorporated into DNA in the

place of thymidine after phosphorylation, and the latter inhibits viral and cellular DNA polymerase after it is phosphorylated. Neither drug has any effect on any other family of DNA virus in vivo.

The latest class of antiviral drug to be approved for use in man is *acycloguanosine* (*Acyclovir*[®]). This drug is unique in that it is effective against herpesvirus-infected cells because it requires the activity of a virus-specified thymidine kinase in order to be phosphorylated. In the latter form, it becomes a competitive inhibitor of DNA polymerase (more of viral than of host DNA polymerase).⁹

Unfortunately, none of these compounds approaches the effectiveness of antibiotics for many reasons, and none of these compounds can be used in pregnancy because of their effects on cellular nucleic acid metabolism. A large number of other drug classes are being used experimentally in cell culture and animal models, many of which show promise for clinical trials. Some of these, such as interferon and its inducers, are currently undergoing clinical testing. The era of antiviral therapy is only beginning, and in the future, we should see a whole new spectrum of therapeutic compounds so that one can reach for the specific drug just as one reaches for the specific antibiotic.¹⁰

The most successful control measures for viral infection in man have been the utilization of vaccines for active immunization. This was demonstrated first for smallpox in the 18th century by Jenner but was not used for any other virus until the early 20th century, when Pasteur successfully immunized people with live, attenuated rabies vaccine. Next came killed and live, attenuated poliovirus vaccines in the 1950s and attenuated measles virus vaccine and killed influenza vaccines in the early 1960s. These were followed by live, attenuated rubella and mumps vaccines. The latest vaccines developed for clinical use are an improved rabies vaccine and a killed vaccine against hepatitis B. In addition to active immunization against viral infection, as illustrated by the vaccines mentioned here, there have been a number of hyperimmune globulins developed for such virus infections as hepatitis B, varicella-zoster, and rabies. These globulins provide effective passive immunization.

Future activity in the control of viral infection will be a continuation of these same three measures—prevention of vector transmission, improved antiviral drugs, and new and improved vaccines for active and passive immunization.

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77. GENERAL CONSIDERATIONS OF VIRAL RESPIRATORY DISEASES

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DEFINITION

Viral respiratory illnesses are ubiquitous in the general population. Syndromes of mild-to-moderate illness characterized by generalized malaise, fatigue, coryza, and cough are usually endemic in the community during the winter months. These nonspecific upper respiratory infections are commonly seen in preschool and grammar-school children and are often brought home by these children to their pregnant mothers. Many viral respiratory illnesses are clinically trivial and are not responsible for any significant morbidity. Pregnant women, however, often report the occurrence of a viral respiratory illness during their gestation and are concerned about its potential impact on their pregnancy and on the fetus they are carrying.

ETIOLOGY

Viral respiratory illness can be caused by a large number of viruses belonging to several different taxonomic groups. Although some of these viruses cause characteristic syndromes that allow presumptive diagnosis on clinical grounds, the overlap of clinical symptoms is great. The groups of viruses most commonly associated with acute viral respiratory disease are indicated in Table 77-1. They include influenza, adenoviruses, parainfluenza viruses, respiratory syncytial virus, the rhinovirus group of picornaviruses, and coronaviruses.¹ Respiratory illnesses are less commonly associated with enterovirus infection. In immunocompromised patients, DNA viruses such as herpes simplex virus, varicella-zoster virus, and cytomegalovirus may cause pneumonia. Pregnant women at term may be at increased risk for varicella pneumonia.

PATHOGENESIS AND PATHOLOGY

Acute viral respiratory infections are generally limited in the pathophysiological changes they produce. The

initial site of virus replication is in the nasopharyngeal mucosa, which is infected when the patient inhales droplet nuclei created by the sneezing and coughing of other affected individuals. The viruses multiply locally, and there is little further dissemination of virus either contiguously to the lower respiratory tract or systemically through viremia. The most common viral respiratory illnesses, because they are not associated with a viremic phase, are not associated with any direct fetal infection. Therefore, one might expect the incidence of fetal wastage and congenital malformations to be small. As a group, these viruses have not been associated with any increased incidence of fetal complications of pregnancy with the possible exception of influenza during major epidemics.^{2–5} Influenza is discussed in greater detail in Chapter 79.

Acute viral respiratory illnesses, although generally trivial, may be responsible for some respiratory embarrassment in pregnant women late in their gestations. Although the degree of respiratory compromise secondary to these viruses may be small, it may compound the normal physiological mechanical limitation of maternal ventilation by the fetus. Women at term have decreased functional residual capacities despite the fact that minute ventilation may be maintained or, in fact, increased.^{6,7} Compromise of their pulmonary function, however slight, by direct viral infection of the respiratory mucosa and/or increased demands for ventilation in response to an acute illness may cause pregnant women more respiratory distress than otherwise healthy nonpregnant females.

Women suffering from viral respiratory infections during pregnancy may take a variety of medications for relief of symptoms of their illness, with or without a physician's recommendation. The safety of most drug use in pregnancy has not been adequately evaluated. Respiratory infections may affect maternal and fetal outcome indirectly through side effects of concurrent drug use. For instance, the increased incidence of central nervous system malformations associated with 1957–1958 influenza