Human Immunodeficiency
Virus and the Placenta

Current Concepts of Vertical Transmission
in Relation to Other Viral Agents

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ABSTRACT

The prevalence of human immunodeficiency virus (HIV) infection in women of the reproductive age group has been increasing and, with it, vertical transmission of the virus to their infants. It is currently believed that intrauterine transplacental infection of the fetus is the most important mechanism of vertical transmission; thus, a recent focus of investigation has been on the role of the placenta in maternofetal HIV infection. However, the mechanisms by which infectious agents cross the placenta to infect the fetus remain largely unknown. Some lessons of possible relevance to issues related to vertical HIV transmission may be gained by reviewing the experience with other agents that can affect the fetus and newborn. This communication examines current virologic and clinicopathologic features of perinatal HIV infection in light of concepts of placental and fetal infection with other viral agents in an attempt to find a model of vertical HIV transmission.

Introduction

In 1983 a newly-recognized virus, now termed the human immunodeficiency virus type 1 (HIV), was documented to result in development of the acquired immunodeficiency syndrome (AIDS) in offspring of infected women. Since then, the prevalence of HIV infection in women of the reproductive age group has increased and, with it, vertical transmission of the virus to their infants. Pediatric HIV infection now closely reflects the spread the HIV infection in young women, disproportionately from minority backgrounds in the United States, who are intravenous drug users or who have sexual relations with intravenous drug-using males. The magnitude of this problem has become a major public health concern. Recent studies from New York and Massachusetts indicate that up to two percent or more of live

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births in some areas of the United States occur in women with HIV infection, and the incidence is higher in other parts of the world. By 1992, it has been estimated that there will be at least four million cases of HIV infection in women and one million in children throughout the world. There is currently no curative treatment or vaccination available for this infection.

Approximately 80 percent of pediatric cases of AIDS in the United States are believed to arise from vertical transmission. Although this may occur by several routes, including intrapartum transmission and breast feeding, it is currently believed that intrauterine transplacental infection of the fetus in utero is the most important mechanism of vertical transmission. Consequently, a recent focus of concerted investigation has centered around the role of the placenta in maternofetal HIV transmission, as well as the related pathogenetic and immunologic mechanisms which may permit fetal infection. As the vital link between the mother and her conceptus, the placenta can provide the pathway for some, but not all, agents to infect the fetus or newborn. Although a wide variety of microbial agents of several classes, including viruses, bacteria, parasites and fungi, can be transmitted from mother to fetus in utero, little is currently known of the mechanisms for transplacental infection.

Two important corollary questions which arise from epidemiologic observations of perinatal HIV infection are: (a) what are the factors during pregnancy (maternal, placental, and fetal) which permit HIV transmission to approximately one of four infants at risk? and (b) what proportion is a result of transplacental, intrapartum, or post-natal (e.g., breast feeding) transmission? It may be helpful to examine several features of other perinatal viral infections in order to understand the mechanisms of transplacental HIV infection. This communication attempts to discover analogies from other viruses which may be a model for vertical HIV transmission and reviews current concepts of HIV infection and the placenta.

Analogies with Perinatal Viral Infections

MECHANISMS OF TRANSPLACENTAL INFECTION

Infectious agents can affect the placenta by two major mechanisms. Those microbes which inhabit the maternal vagina or cervix can, by ascending infection, reach the placenta. Ascending infections are characterized microscopically by inflammation of the placental membranes, and result in chorioamnionitis. However, this mechanism is an uncommon route of maternofetal transmission of viral agents, with the herpes simplex viruses the only major viral agents to infect the fetus by this pathway.

Fetal infection via the placenta may also occur hematogenously, whereby microbes present in the maternal bloodstream enter the placenta via endometrial vessels. This route of infection is the major mechanism of maternofetal transmission for most viral agents which can infect the fetus, as well as certain other microbes including bacteria (Listeria monocytogenes, Treponema pallidum) and parasites (Toxoplasma gondii, Trypanosoma cruzi). However, the mechanisms by which infectious agents cross from the maternal circulation into the placental chorionic villi and, subsequently, the fetus remain largely unknown.

Not all viruses infecting pregnant women can result in transplacental infection of the fetus. Intrauterine transmis-
sion of mumps, measles, variola, varicella, influenza, enteroviruses, hepatitis A and B, rabies, and herpes simplex viruses are uncommon (table I). Current evidence suggests that HIV can result in fetal infection in approximately 15 to 30 percent of infants of seropositive mothers and that probably at least half are transplacentally transmitted.14,22,38

What is currently known of the conditions which permit some, but not all, maternal infections to result in transplacental infection? First, the agent must be present in the maternal bloodstream during at least part of its life cycle. In table I, the capability for the various viruses to result in transplacental infection is compared with the frequency of maternal infection and presence of virus in the maternal circulation. It can be seen that the major perinatal-acquired viral infections, i.e. cytomegalovirus (CMV), rubella virus, and parvovirus B19, have in common with HIV the presence of circulating virus in the maternal blood. This may explain why two major members of the herpes virus group, cytomegalovirus (CMV) and herpes simplex virus (HSV), show different propensities for fetal infection. Both viruses are of similar size; however, CMV is frequently present in the blood and readily crosses the placenta to infect the fetus. In contrast, HSV is not typically found in the circulation and intrauterine fetal infection is rare.3,40,43 The presence of virus in the blood may not be sufficient since two other herpes viruses, the Varicella-Zoster and Epstein-Barr viruses, infrequently infect the fetus.

The mechanism for viral entry into the fetal circulation of the placenta is of critical importance in development of a model for intrauterine HIV infection. Examination of the anatomical features of the chorionic villus, through which a microbial agent must pass to gain entry to the fetus, reveals three major tissue barriers between maternal and fetal circulations. In sequential order from maternal to fetal sides, these include: (1) the trophoblast and its basement membrane, (2) mesenchymal tissue core of the chorionic villus including the villous macrophages, termed “Hofbauer cells,” and (3) the basement membrane and endothelial cells of the fetal villous capillaries (figure 1). Several of these fetal-derived tissues, including Hofbauer cells and perhaps trophoblasts, contain CD4, a receptor for HIV.33,36 Unfortunately, the mechanism by which viruses cross these barriers remain largely unknown. However, several means have been described by which other substances can cross the placenta: simple and facilitated diffusion;

| TABLE I  
<p>| Transplacental Transmission of Viruses |</p>
<table>
<thead>
<tr>
<th>Maternal Infection</th>
<th>Viruses Frequently Found in the Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Viruses Found to Infect the Fetus Commonly</strong></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>+</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>(+)</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>B. Viruses Found to Infect the Fetus Uncommonly</strong></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex viruses</td>
<td>(types 1 &amp; 2)</td>
</tr>
<tr>
<td>Varicella virus</td>
<td>-</td>
</tr>
<tr>
<td>Varicella-vaccinia</td>
<td>-</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>(+)</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>(+)</td>
</tr>
<tr>
<td>Measles virus</td>
<td>(+)</td>
</tr>
<tr>
<td>Mumps virus</td>
<td>(+)</td>
</tr>
<tr>
<td>Rabies virus</td>
<td>-</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>C. Viruses Not Yet Determined to Infect the Fetus</strong></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>+</td>
</tr>
<tr>
<td>Herpes viruses 6 &amp; 7</td>
<td>+</td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>(+)</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>?</td>
</tr>
<tr>
<td>T cell leukemia retrovirus</td>
<td>(+)</td>
</tr>
</tbody>
</table>

(+): Epidemic or seasonal
HIV Virions \textit{(extracellular in plasma)}

- Few
- Many

Coated with IgG molecules

Cell–Associated HIV

- Lymphocytes/monocytes

+/- IgG molecules

Maternal Blood

HIV in fetal blood

What form

Breaks

Maternal blood

Bacterial and viral transport; and breaks in placental villi. It is unlikely that either diffusion processes or bulk transport occur with viruses. A more likely mechanism, breaks in the trophoblastic layer, may result from injury to the chorionic villi by a diverse group of factors, including vascular insufficiency, trauma, or co-existing inflammatory conditions including infections.

**Villositis and Chorioamnionitis**

Accompanying most maternal blood-borne infections which infect the placenta is the finding of inflammation of the chorionic villus, termed villitis.\(^3\) This histopathologic hallmark of hematogenous infection may be (1) acute, consisting of predominantly neutrophils, (2) chronic, consisting of lymphocytes and/or plasma cells, and (3) granulomatous, associated with histiocytes or epithelioid cells. Frequently, a combination of these histological patterns is present. In general, viral infections are associated with lymphoplasmacytic villitis, with the most common example being CMV.\(^4\) However, the few studies which have been reported of the histopathology of placentas from HIV seropositive women have failed to demonstrate either villitis or a consistent microscopic lesion.\(^6,23,37,50\) Both acute and chronic villitis have been identified by the current authors in several placentas of HIV-infected women (see Current Knowledge of HIV and the Placenta) (figure 2); however, this finding appears uncommon.\(^45\) In this regard, it appears that HIV resembles most closely parvovirus B19, in which transplacental infection occurs with only rare reports of the occurrence of villitis.\(^3\) These features may also be
shared with hepatitis B which, although only rarely transmitted transplacentally, is not associated with villositis.\textsuperscript{3}

An interesting pathologic feature of placentas of HIV seropositive women is the frequent finding of chorioamnionitis.\textsuperscript{23,45} As previously stated, this is not usually seen in viral infections but is more typical of infection with other classes of microbial agents.\textsuperscript{3} Although it cannot be stated with certainty, this may be the result of the frequent co-existing infections which HIV-seropositive women are at high risk of developing.\textsuperscript{30}

**Virus-Cell Association**

Another factor which may be important in determining the ability of a virus to infect the placenta is its existence as a free virion or association with a cell. As can be seen in table II, HIV is similar to CMV in that both viruses can be present in the mother's circulation as free virus or in association with maternal leukocytes such as monocytes or lymphocytes. When present in the bloodstream, HIV is predominantly cell-associated after the very early phases of infection and often is in cell-free form late in the course of infection. However, the placenta generally protects the fetus from most viral agents which circulate in maternal blood in association with leukocytes. It seems unlikely, however, that transplacental infection occurs via cell-associated virus, since maternal leukocytes appear only rarely to pass to the fetal circulation.\textsuperscript{20,31}

Thus, extracellular virus may be the most likely form of HIV which could infect the fetus. It is also possible that different strains of virus possess different "tropisms" with respect to placental passage, especially since with HIV infection the infection of monocytes versus lymphocytes appears to be strain-specific.\textsuperscript{34}

**Immunoglobulin Transport and Viral Transmission**

An additional factor to consider is the impact which normal mechanisms of transplacental transport of IgG may have on viral transmission. Organelle-
TABLE II

<table>
<thead>
<tr>
<th>Viruses with Possible Analogies to Human Immunodeficiency Virus</th>
<th>HIV</th>
<th>CMV</th>
<th>HEP B</th>
<th>HSV</th>
<th>HTLV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic or persistent maternal infection in the presence of antibodies</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Commonly found in the vagina-cervix</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Commonly found in the blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. as virion</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>?</td>
</tr>
<tr>
<td>B. as cell-associated virus</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Commonly cause disease in the fetus and/or neonate</td>
<td>+</td>
<td>only primary infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission mode</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Transplacental</td>
<td>+</td>
<td>+</td>
<td>not often</td>
<td>rare</td>
<td>?</td>
</tr>
<tr>
<td>B. Intrapartum: from genital site</td>
<td>?</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>o</td>
</tr>
<tr>
<td>from blood</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>0</td>
<td>o</td>
</tr>
<tr>
<td>C. Postpartum: from breast milk</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>from other infants</td>
<td>?</td>
<td>+</td>
<td>0</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

Viruses with similar evolutionary characteristics as HIV

- HIV - human immunodeficiency virus
- HEP B - hepatitis B virus
- HTLV-1 - T cell leukemia retrovirus
- CMV - cytomegalovirus
- HSV - herpes simplex virus

mediated transport of substances across the placenta is well-exemplified by the passage of IgG. Receptors for the Fc of IgG have been found in the syncytiotrophoblast and in the Hofbauer cells.\textsuperscript{12,17} The reason that different classes of IgG are found in varying amounts of the fetal side of the placenta, and the inability of other classes of immunoglobulins (IgD, IgM, IgE, IgA) to be transported, is most likely a result of the different affinity of the placental Fc receptors for the Fc region of different immunoglobulin isotypes.\textsuperscript{10} Whether Hofbauer cells, which possess Fc receptors,\textsuperscript{12,17} are involved in transport of maternal IgG to the fetus is still speculative. However, it is possible that IgG-coated viral particles may have the potential to attach to the trophoblast via Fc receptors, and thus gain access to the fetal environment.

**HOFBAUER CELLS AND VIRAL PATHOGENESIS**

The role of Hofbauer cells, macrophages believed to be of fetal origin and present in the mesenchymal core of the chorionic villi,\textsuperscript{7} is also of interest in viral pathogenesis. Hofbauer cells may be important in protecting the fetus from IgG complexed to antigens. In the case of IgG-HIV complexes, however, if the Hofbauer cells behave similarly to other macrophages, HIV might replicate or remain latent intracellularly.\textsuperscript{15} Another possibility is that HIV-antibody immune complexes could dissociate, and the virus be released to infect other cells. As Hofbauer cells possess CD4 receptors,\textsuperscript{17,36} they are thus likely candidates for infection by the virus even when not complexed with IgG. Similar to other phago-
cytic cells, Hofbauer cells are probably motile, and occur in sufficient numbers potentially to permit the transfer of HIV to other cells. Additionally, these cells have been suggested to be self-replicating, possibly allowing the diffusion of HIV infection throughout the placenta. Several studies have demonstrated HIV viral material within placental macrophages, and these cells have additionally been implicated in the intrauterine transmission of a protozoal agent, Trypanosoma cruzi.

ROLE OF MATERNAL ANTIBODIES IN PLACENTAL INFECTION

The apparent transmission of HIV from mother to fetus in the presence of circulating maternal antibodies to the virus is interesting. In the case of some viral infections, including rubella, maternal antibody is protective and, as a result, fetal infection can only occur in the non-immune, seronegative pregnant woman. With some other viruses, e.g., cytomegalovirus, the most serious fetal infections occur only after primary infection of a non-immune woman. Although fetal infections with CMV may occur following a recurrent maternal infection in the presence of maternal antibodies, they are usually asymptomatic. Currently, the role of maternal neutralizing antibody in protecting the fetus from HIV transmission is unknown. Maternal IgG regularly begins to cross the placenta in the second trimester. This may be significant in determining whether early intrauterine HIV exposure is more likely to result in an infected fetus. However, the time at which CD4-positive cells become available for viral absorption in fetal life may also be a determinant. Several factors for increased risk of vertical HIV transmission, associated with maternal antibody status, have been reported, including elevated maternal serum IgA concentration and low maternal anti-gp120 titers. Whether or not antibodies to specific peptides of gp120 in the V3 region may influence viral transmission is currently controversial.

INTRAPARTUM AND POSTPARTUM TRANSMISSION OF HIV

Besides in utero transplacental transmission, viral infection of the fetus may occur following contamination with maternal blood or cervical secretions at the time of delivery, termed intrapartum transmission, as well as by breast milk. Those viruses associated with these modes of infection are summarized in tables II and III. Intrapartum transmission is the major route of vertical infection for several medically important viruses, notably hepatitis B, herpes simplex, echoviruses, and coxsackieviruses. This mechanism of infection is theoretically possible for HIV, as virus has been isolated from vaginal and cervical secretions in approximately 50 percent of infected adult women. Although difficult to prove, no cases of vertical transmission of HIV have been shown to occur by this mechanism. Another mechanism of infection, post-partum transmission by

<table>
<thead>
<tr>
<th>TABLE III</th>
<th>Viruses Associated with Modes of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTRAPARTUM</strong></td>
<td><strong>Main Mode of Transmission</strong></td>
</tr>
<tr>
<td>Herpes simplex viruses (Types 1 &amp; 2)</td>
<td>Genital infection</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Cervical infection</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Blood</td>
</tr>
<tr>
<td><strong>BREAST MILK</strong></td>
<td><strong>Frequency of Transmission</strong></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Common</td>
</tr>
<tr>
<td>T cell leukemia retrovirus</td>
<td>Common</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Herpes simplex viruses</td>
<td>Very infrequent</td>
</tr>
</tbody>
</table>
infected breast milk, may occur with CMV as well as another retroviral infection, human T-cell lymphotrophic virus-1 (HTLV-1). Similar to these viruses, HIV has been isolated from breast milk and colostrum, and several case reports of pediatric HIV infection from breast milk have been described.

Current Knowledge of HIV and the Placenta

Currently there is a serious deficiency of knowledge concerning the role of the placenta in the vertical transmission of HIV. At the macroscopic level, placentas from HIV-infected partrurients fail to demonstrate any distinguishing lesions compared to non-infected controls. The few studies published to date of the microscopic features of placentas from HIV-infected women have failed to reveal any consistent abnormalities. However, a trend toward increased placental weight has been noted, as well as the observation of "hypermaturity" and an excess of fibrinoid deposition and calcifications. These findings are, however, nonspecific. Schwartz et al are the only investigators to demonstrate villitis associated with HIV infection. In this study of placentas from 24 HIV-seropositive pregnant women, the infection status of 16 infants was known, while the status of eight infants was unknown. None of the 12 placentas from uninfected infants showed abnormalities of chorionic villi or decidua, although six had chorioamnionitis. One of the four placentas from HIV-infected infants had chronic villitis of unknown etiology, associated with lymphoplasmacytic deciduitis (figure 2). Two of eight placentas from infants whose infectious status was still indefinite also had villitis of unknown etiology. The significance of this finding in light of HIV infection remains speculative.

There is convincing evidence that both the placenta and fetus can become infected with HIV early in pregnancy. Human immunodeficiency virus has been cultured from the umbilical cord blood of infants and from amnionic fluid. Several studies have demonstrated that fetal intrauterine infection may occur in gestation. Human immunodeficiency virus has been recovered in cell culture from fetuses aborted at nine and 20 weeks gestation. Courgnard et al found HIV DNA in 19 of 31 thymic samples and 22 of 33 spleen samples of 16 to 24 week gestational age fetal tissues using the polymerase chain reaction (PCR). Human immunodeficiency virus antigen has also been identified in placental tissues. In one study, HIV core antigens were detected in approximately 50 percent of placental tissues of infected mothers and could be localized in the placental macrophages. Lewis et al localized HIV antigens and nucleic acid in placental tissues from three infected women having therapeutic abortions at eight weeks gestation. In this study, maternal decidual leukocytes, trophoblast, villous endothelial cells, and Hofbauer cells were all found to be positive for viral material. Mattern et al identified HIV antigen in 13 of 25 placentas from seropositive women using a monoclonal antibody to p24 antigen. This antigen was detected only in those cells having the morphology of macrophages in chorionic villi. The variability in the data attempting to localize HIV antigens and nucleic acids in placental tissues reported by several groups at the Sixth International Conference on AIDS lends caution to the interpretation of results obtained with these methods.

Summary

Some lessons of possible relevance to issues related to vertical HIV transmission may be gained by reviewing the
experience with other agents that can affect the fetus and newborn. Therefore, this communication has examined current virologic and clinicopathologic features of HIV infection in light of concepts of placental and fetal infection with other viral agents in an attempt to find a model of vertical transmission. As summarized in Table II, it has been noted by us that, although certain facets of perinatal HIV infection have analogies with other vertically-transmitted viral infections of the placenta and fetus, there is no single agent which more than superficially resembles HIV infection in pregnancy. Thus, the authors have been unable to find a satisfactory model amongst other vertically-transmitted viral infections for the pathogenesis of pediatric HIV transmission. There remains little doubt that in utero transmission of HIV from mother to fetus is a significant mechanism of vertical transmission; however, the role of the placenta remains unknown. Further studies using both conventional and innovative technologies will be necessary to increase our understanding of the pathogenesis of vertical HIV infection.

References


Human immunodeficiency virus and the placenta

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