Many different viruses can infect placental cells and are associated with congenital infection (Table 1). Viruses such as rubella, cytomegalovirus (CMV) and parvovirus are recognised as infectious agents of the placenta and foetus. Herpes simplex virus (HSV), varicella, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and enterovirus occasionally infect the placenta and foetus, but are more commonly known as perinatal pathogens. Other viruses such as adenovirus and adeno-associated virus (AAV) have been found to infect the placenta, but a causative link between viral infection and poor pregnancy outcome has not yet been definitively established. Viral infection of the placenta is predominantly defined by the permissiveness of placental trophoblast cells to specific viruses. In the development of the placenta, trophoblast cells differentiate into mononucleated cytotrophoblast cells that invade maternal tissues or fuse into multinucleated syncytiotrophoblasts that cover the villous surface. The cytotrophoblast and syncytiotrophoblast layers are quite distinct during the first trimester and this distinction gradually diminishes as gestation progresses. Placental villi form a continuous layer and are the site for exchange between the maternal and

Table 1. Viruses associated with congenital infection.

<table>
<thead>
<tr>
<th>Virus (Abbrev)</th>
<th>Maternal disease</th>
<th>Congenital infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Generally asymptomatic</td>
<td>Major known causative agent of viral congenital infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Causes significant foetal anomalies, deafness and foetal death</td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV)</td>
<td>Cold sores, genital herpes</td>
<td>Spontaneous miscarriage and neonatal death</td>
</tr>
<tr>
<td>Varicella Zoster Virus (VZV)</td>
<td>Chickenpox</td>
<td>Significant foetal anomalies and foetal death</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Erythema infectiosum</td>
<td>Foetal hydrops, foetal anaemia, stillbirth and preterm birth</td>
</tr>
<tr>
<td>Coxsackie A and B</td>
<td>Various presentations</td>
<td>Neurodevelopmental delay and spontaneous miscarriage</td>
</tr>
<tr>
<td>Enterovirus (EV)</td>
<td>Various presentations</td>
<td>Neurodevelopmental delay, stillbirth and diabetes</td>
</tr>
<tr>
<td>Echovirus</td>
<td>Various presentations</td>
<td>Neurodevelopmental delay and foetal death</td>
</tr>
<tr>
<td>Rubella</td>
<td>German measles</td>
<td>Stillbirth, cerebral palsy and neurodevelopmental delay</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Various presentations</td>
<td>Intrauterine growth restriction and foetal hydrops</td>
</tr>
<tr>
<td>Adeno-associated virus (AAV)</td>
<td>Unknown</td>
<td>Prematurity and spontaneous miscarriage</td>
</tr>
<tr>
<td>Hepatitis B Virus (HBV)</td>
<td>Hepatitis, cirrhosis</td>
<td>Possible cause of preterm labour</td>
</tr>
<tr>
<td>Human Immunodeficiency Virus (HIV)</td>
<td>Acquired immunodeficiency syndrome</td>
<td>Foetal death</td>
</tr>
<tr>
<td>Lymphocytic Choriomeningitis Virus (LCMV)</td>
<td>Lymphocytic choriomeningitis</td>
<td>Significant foetal anomalies and hydrops</td>
</tr>
</tbody>
</table>
Infections may downregulate HLA-C and HLA-G expression in some cell lines, but not others, and placent al infection with HSV may also decrease cellular HLA-G expression. Downregulation of these MHC molecules may make infected trophoblasts a target for NK cells, which could lead to cell death and placental dysfunction.

Viral infection of trophoblasts can therefore impair placental cell development and function and have adverse effects on pregnancy outcome, without foetal infection occurring. Adenovirus infection is known to increase apoptotic cell death and both adenovirus and CMV have been shown to impair the ability of trophoblasts to differentiate and invade.

The exact mechanisms by which viruses cause such cellular responses are not known and it is not clear if these responses are viral specific. However, cellular apoptosis, reduced invasiveness and reduced cellular functions can all compromise implantation in the uterus or the formation of placental villi. Such impairment of placental development can have serious consequences on the pregnancy, such as intrauterine growth restriction, preterm labour and spontaneous miscarriage.

As protection against some viral infections, the placenta has naturally high levels of cytokines. Placental inflammation and increased levels of specific interferons, however, are considered risk factors for cerebral palsy. Inflammation and other immune reactions are induced by viral infections and, indeed, prenatal infection with rubella is a known cause of cerebral palsy. Research into an association between cerebral palsy and placental infection with other viruses has not yet been conducted, but it is interesting to speculate that unexplained cases of cerebral palsy or other disorders not normally attributed to viral infection, may have been caused by a sub-clinical viral infection of the placenta.

In the past, viral infections of the placenta have been poorly described for a number of reasons - viruses are difficult to culture, results from histological studies are often non-specific, and pathological findings in the placenta correlate poorly to neonatal outcome. The use of molecular techniques has more recently alleviated some of these problems.

The association between placental viral infection (as opposed to foetal viral infection) and adverse pregnancy outcome still remains to be clarified by large prospective studies. Such studies have yet to be conducted due to the obvious difficulties in setting up a study with adequate statistical power.

Multiple viral testing of placental tissue by molecular methods should be uniformly encouraged and would be especially informative in cases in which the causative agent is unknown and the histological findings are non-specific. The information obtained from such tests would help to clarify the frequency of viral placental infections and their overall role in adverse pregnancy outcome.

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References


