Viruses in the placenta

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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[13]. 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.

Virus (Abbrev)	Maternal disease	Congenital infection
Cytomegalovirus (CMV)	Generally asymptomatic	Major known causative agent of viral congenital infection Causes significant foetal anomalies, deafness and foetal death[1]
Herpes Simplex Virus (HSV)	Cold sores, genital herpes	Spontaneous miscarriage and neonatal death[2]
Varicella Zoster Virus (VZV)	Chickenpox	Significant foetal anomalies and foetal death[3]
Parvovirus B19	Erythema infectiosum	Foetal hydrops, foetal anaemia, stillbirth and preterm birth[4]
Coxsackie A and B	Various presentations	Neurodevelopmental delay and spontaneous miscarriage[5]
Enterovirus (EV)	Various presentations	Neurodevelopmental delay, stillbirth and diabetes[5, 6]
Echovirus	Various presentations	Neurodevelopmental delay and foetal death[6]
Rubella	German measles	Stillbirth, cerebral palsy and neurodevelopmental delay[7]
Adenovirus	Various presentations	Intrauterine growth restriction and foetal hydrops[8]
Adeno-associated virus (AAV)	Unknown	Prematurity and spontaneous miscarriage[9]
Hepatitis B Virus (HBV)	Hepatitis, cirrhosis	Possible cause of preterm labour[10]
Human Immunodeficiency Virus (HIV)	Acquired immuno-deficiency syndrome	Foetal death[11]
Lymphocytic Chorio-meningitis Virus (LCMV)	Lymphocytic choriomeningitis	Significant foetal anomalies and hydrops[12]

foetal circulations. Viruses may infect the developing placenta through cell-to-cell transfer or alternatively may be transmitted through maternal blood.

Most viruses associated with congenital infection have demonstrated the ability to infect placental trophoblast cells [14-18]. Differentiation of cytotrophoblasts into syncytiotrophoblasts appears to affect the permissiveness of the cells to viral infection. Congenital rubella infection and its symptoms are significantly reduced if infection occurs after the first trimester [7]. In contrast, the occurrence of congenital CMV increases with progressive gestation, although the severity of the infection is reduced [1]. *In vitro* studies have shown that syncytiotrophoblasts are more resistant than cytotrophoblasts to infection by some viruses (adenovirus, HSV and HIV) but not others (AAV and CMV) [16, 19, 20]. Cellular receptors involved in viral binding and cell entry are thought to play a major role in the variation seen in cellular susceptibility [18-20].

The ability of viruses to infect placental cells and avoid the host's immune defences may rely, in part, on some of the mechanisms the foetus employs to avoid allogenic recognition. Classical major histocompatibility complex (MHC) class 1 molecules (HLA-A and HLA-B) are important in antigen presentation to T cells and natural killer (NK) cells. These MHC molecules are ubiquitously expressed in human cells, with the exception of placental cells. In place of these molecules, some trophoblasts express the classical MHC class 1 molecule HLA-C, as well as non-classical MHC class 1 HLA-G and HLA-E molecules. These molecules are thought to moderate the immune response to the trophoblast cells, but the exact mechanism by which this occurs is not known.

In vitro studies have shown that CMV infection may downregulate HLA-C and HLA-G expression in some cell lines [21], but not others [22], and placental infection with HSV may also decrease cellular HLA-G expression [23]. Downregulation of these MHC molecules may make infected trophoblasts a target for NK cells, which could lead to cell death and placental dysfunction [24].

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 [20, 25].

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 cellar 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 [26]. Placental inflammation and increased levels of specific interferons, however, are considered risk factors for cerebral palsy [27, 28]. Inflammation and other immune reactions are induced by viral infections and, indeed, prenatal infection with rubella is a known cause of cerebral palsy [29]. 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 [14, 17]. 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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