Longer-term outcomes of infections in pregnancy: pathogenesis of diabetes and other chronic infections

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Rubella and cytomegalovirus (CMV) are recognised causes of congenital diabetes. The role of *in utero* infection with other viruses, such as enteroviruses (EV), in the development of childhood diabetes is less clear. Epidemiological studies have demonstrated an association between maternal EV infection and subsequent development of type 1 diabetes in their offspring, suggesting that the disease process begins *in utero*.

Congenital infection with viruses such as Rubella and CMV may result in severe long-term sequelae, including developmental delay, hearing loss, cerebral palsy, epilepsy and diabetes [1]. CMV is the most common cause of viral-induced congenital malformation – primary CMV infections occur in up to 2% of pregnant women, with 30-40% of mothers vertically transmitting the virus to the fetus. The virus may be transmitted *in utero* during primary maternal infection, or by reactivation or reinfection of seropositive mothers. While most (85-90%) of congenital CMV cases are asymptomatic at birth, 10-15% will develop symptoms in later life, the most common being sensorineural hearing loss.

Infection with rubella virus during the first 12 weeks of pregnancy results in congenital infection and/or miscarriage in 80-90% of cases. The congenital rubella syndrome involves multiple organ systems, with a long period of active infection and virus shedding in the postnatal period. The syndrome includes a range of malformations, including sensorineural deafness, cataracts, cardiac anomalies and mental retardation, with late complications including diabetes, thyroid disease, growth hormone deficiency, and progressive panencephalitis.

Congenital forms of virus induced diabetes result from direct infection of the pancreatic ß-cells which may be chronic. Certain viruses are known to be pancreotropic, including mumps [2], rubella [3] and picornaviruses [4]. In the case of congenital rubella

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syndrome, overt disease can develop after more than 20 years following *in utero* infection [3]. Congenital CMV infection is also thought to result in late development of diabetes [5]. In these relatively uncommon cases, the process is probably due to gradual ß-cell destruction rather than an autoimmune process. However, an association was found between CMV infection and islet cell antibodies in patients with newly diagnosed diabetes [6], suggesting that persistent CMV infection (but not necessarily congenital) can lead to autoimmune diabetes.

The majority of children who develop diabetes have type 1 (insulin dependent) diabetes, a condition that affects approximately 1 in 700 children aged <15 years. This is an autoimmune disease caused by destruction of the insulin producing ß-cells in the pancreas, which is probably mediated by autoreactive T-cells. The risk of developing type 1 diabetes is to some extent genetically determined, but environmental factors also appear to be involved in the autoimmune process. Indeed, the rapid increase in the incidence of type 1 diabetes during recent years, particularly in Australia [7,8], is highly supportive of a major role for environmental factors in the disease process.

EVs, in particular Coxsackie virus B4 (CVB4), are the most widely studied and likely environmental triggers of ß-cell autoimmunity and type 1 diabetes. Higher rates of enterovirus infection have been demonstrated in children at onset of type 1 diabetes, in particular amongst those who do not have diabetes associated risk genes [9]. An increased number of enterovirus infections have been found in pre-diabetic children in several prospective studies using serological tests and enterovirus RNA detection [10]. Enterovirus infections during pregnancy have also been associated with an increased risk of developing type 1 diabetes in the offspring [11], suggesting that the autoimmune process may begin *in utero*. Whilst most studies imply a causal association of enterovirus infection and type 1 diabetes, there are also several studies demonstrating direct infection of ß-cells in humans with type 1 diabetes [4,12].

Several mechanisms for the induction of ß-cell destruction by viruses have been suggested. Viruses may also cause a direct cytolysis of infected ß-cells or induce bystander activation of autoreactive T-cells due to the inflammatory mediators released in infected islets, or alternatively the process may be due to molecular mimicry, whereby viral antigens cross react with ß-cell antigens and induce autoreactivity.

Whilst there is currently limited evidence that enterovirus infection *in utero* is an important cause of childhood onset diabetes, prospective studies of infants at genetic risk of type 1 diabetes, such as the international studies TRIGR, DAISY and TEDDY, and the VIGR study in NSW, may help to address the role of virus infections early in life.

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