Protozoan and helminth infections in pregnancy. Short-term and long-term implications of transmission of infection from mother to foetus

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SUMMARY

This review of protozoan and helminth infections in pregnancy focuses on the impact on the immune response in the newborn infant to maternal infection. Studies of protozoan and helminth infections in pregnant women and in their offspring have shown that children exposed to antigens or microorganisms during pregnancy often have a reduced immune response to these infections. The most common finding is a reduced IFNγ response to specific antigens regardless of specific infection studied. In some studies the impaired immune response disappeared before the age of one year, while in other studies the impaired immune response was present as much as two decades after birth. Data from chronic viral infections like Rubella, cytomegalovirus and hepatitis B also show that congenital or perinatal infections may result in a life-long inability to control the infections. Studies of both helminth and protozoan infections show that children exposed to antigens during gestation have a microorganism-specific impaired immune response which is characterized by reduced IFN-γ and stimulation of responses to specific antigens.

Key words: Pregnancy, newborns, protective immunity, tolerance protozoa, helminth.

INTRODUCTION

Protozoan and helminth infections in pregnant women are as prevalent as in the rest of the community where those individuals live. Many parasitic infections, both protozoa and helminth, are life-long, chronic infections which cannot be cleared by the host immune system. Chronicity of infections during pregnancy such as schistosomiasis, filariasis, malaria and *Trypanosoma cruzi* mean that the foetus was gestated and breast-fed by a mother with chronic infections. These children have been exposed to parasitic antigens and maternal antibodies *in utero*, which may have modulated their immune response later in life as was demonstrated for different helminth antigens more than twenty five years ago (Weil *et al*. 1983). A decreased IFNγ response to heterologous antigens has been found in children born to mothers with filariasis and schistosomiasis (Malhotra *et al*. 1999). A common observation in many parasitic infections is long-term antigen persistence resulting in a constant simulation of the immune system, and it has been suggested that the lack of ability to control these infections properly is due, in part, to exhaustion of the CD4+ T cell memory pool resulting in insufficient maintenance of CD8+ effector memory T cells (Brake, 2003).

The foetus, neonate and infant are more susceptible to infections than older children and adults. This is considered to be partly due to the immaturity of their immune system especially the ability to generate cell mediated immunity (Adkins, Leclerc and Marshall-Clarke, 2004). Helminth infections influence the immune system of the host and are associated with a down-regulated immune response typically with polarization towards a Th2 response (Maizels and Yazdanbakhsh, 2003; Wilson and Maizels, 2006).

This review discusses data on how maternal and congenital infections affect the parasite-specific immune response in the child and considers the protozoan infections malaria, *Toxoplasma gondii* and *Trypanosoma cruzi* and the helminth infections *Onchocerca volvulus, Wuchereria bancrofti* and schistosomiasis; parallels are drawn to congenital or perinatal viral infections with Rubella virus, cytomegalovirus and hepatitis B virus.

MALARIA

It is well known that the immune system is skewed towards a Th2 response in pregnancy in order to minimize the risk of a 'host versus graft' reaction. This reduces the ability of the pregnant women to fully control some infections compared to non-pregnant women. This has been well documented for

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Plasmodium falciparum malaria (Blacklock and Gordon, 1925; Bray and Anderson, 1979; Brabin, 1983; Bruce-Chwatt, 1983) where a higher parasite density, especially in the second trimester, and a higher spleen rate and enlarged spleen have been found (McGregor, 1984; Brabin *et al*. 1988). Malaria infections during pregnancy contribute to anaemia in the mother, reduced birth weight and premature birth (Cannon, 1958; Gilles *et al*. 1969; Brabin *et al*. 1990; Nosten *et al*. 1991), but immunity to malaria in the pregnant women increases with increasing parity (Desowitz, 1992).

Congenital malaria infections of around 5% have been reported based on microscopy (Covell, 1950; Larkin and Thuma, 1991; Tobian *et al*. 2000), but rates up to 33% have been reported using PCR (Tobian *et al*. 2000; Xi *et al*. 2003), and soluble malaria antigens can cross the placenta from infected mothers to the foetus (Druilhe, Monjour and Gentilini, 1976; Desowitz, 1988; King *et al*. 2002). A study from Malawi found that placental malaria infection was associated with lower perinatal mortality among normal birth weight ($\geqslant$2500 g) infants (OR 0·35, 95% CI: 0·14, 0·92) (McDermott *et al*. 1996). This is difficult to explain, but a reduced immune response leading to diminished pathology could be one possibility. The immune response in the neonate is compromised. A study from Cameroon of cord blood samples from 164 newborns found a highly reduced ability of T cells to secrete IFNγ after exposure to malaria antigens as well as leucoagglutinin, but equal levels of IL-2 and IL-4 (Fievet *et al*. 1996). The same study found an increased risk of children having parasites in the blood if the mother had malaria parasites in the placenta when the child was born (Le Hasran *et al*. 1997; Deloron *et al*. 1997). A study from Tanzania found that children born to multigravida women with placental malaria had a higher risk of parasitaemia compared to multigravida without placental malaria, but found no difference in children born to primigravida or secundigravida mothers (Mutabingwa *et al*. 2005).

A study of the pyrogenic threshold in children and adults found that it was twenty times higher in children compared to adults (Miller, 1958); these data were confirmed in a later study from Liberia, which found a six fold decrease in parasite density in adult patients with a body temperature of $\geqslant$38 °C (Petersen *et al*. 1991). This could be explained by an immune tolerance in children which resulted in reduced control over parasite density but also diminished symptomatology.

The immunological mechanisms that confer the relative inability to control malaria in children born to mothers with placental malaria are not completely understood. A study from The Gambia found poor antigen presenting cell, APC, function in newborn infants born to mothers with placental malaria infection (Ismaili *et al*. 2003). Another study from Cameroon compared children born to mothers treated for malaria during pregnancy with children born to mothers with malaria during pregnancy and found that IL-10(+) T cells *in utero* may contribute to suppression of the APC function and Pf Ag-induced Th1 responses were reduced in infants from mothers with placental malaria (Brustoski *et al*. 2005, 2006). A study of newborn infants in Kenya found that neonates were more likely to have a Th2 response to malaria antigens if born to multigravida mothers compared to primi- and secundigravida mothers, and the authors suggested that active suppression or T-cell anergy to malaria specific antigens developed in some newborn infants (Malhotra *et al*. 2005*a*). Inhibition of co-simulation by dendritic cells has been found in one study (Urban *et al*. 1999) and insufficient costimulatory signals to neonatal T cells from immature antigen presenting cells has also been described (Broen *et al*. 2007). It has been proposed that possible refractoriness to toxin-induced Toll-like receptor mediated signalling is due to cross reactivity between endotoxin and malaria glycosylphosphatiylinositol, GPI (Boutlis *et al*. 2006).

The molecular basis for placental malaria is the sequestration of *P. falciparum*-infected erythrocytes expressing the erythrocyte membrane protein 1, PfEMP1 antigen belonging to the *var* genes (Baruch *et al*. 1997; Su *et al*. 1995). PfEMP1 mediates adhesion to a range of host surface receptors which have been identified as targets for *P. falciparum* binding (Craig and Scherf, 2001). In the placenta, the *P. falciparum*-infected erythrocytes accumulate in the intervillous space (Yamada *et al*. 1989). Both trophozoites and schizonts adhere to the endothelium in the placenta in contrast to other organs where only schizonts adhere (Pouvelle *et al*. 2000). The observations that primigravidae in particular have a high risk for placental sequestration and low birth weight infants, a particular problem in primigravidae with malaria, have lead to much interest in the development of immunity to *var* antigens in particular PfEMP1 (Fried *et al*. 1998; Riecke *et al*. 2000). It is, however, unclear how the sequestration of *P. falciparum*-infected erythrocytes in the placenta results in low birth weight infants. Sequestration of *P. falciparum*-infected erythrocytes results in an inflammatory response in the placenta (Fried *et al*. 1998; Moormann *et al*. 1999). In particular, monocyte infiltration in the placenta has been identified as an important predictor of low birth weight infants (Ordi *et al*. 1998; Menendez *et al*. 2000; Abrams *et al*. 2003; Rogerson *et al*. 2003). A parallel may be drawn to recent results from congenital CMV infection which is associated with an increased thickness of the placenta probably as a result of placental inflammation. In CMV infections, the placental inflammation is partly responsible for the pathology in the child with congenital CMV (Torre *et al*. 2006; Schleiss, 2006). Thus the inflammatory response in

the placenta as a result of malaria infection may be important for the intrauterine growth of the foetus and perhaps also be partly responsible for antigen leakage over the placenta.

TOXOPLASMA GONDII

Congenital infection with *Toxoplasma gondii* is transmitted to about 20% of the offspring. Transmission rates increase with gestation and are below 5% in the first months of pregnancy increasing to approximately 80% in the last few weeks before birth (Dunn *et al*. 1999). Risk of pathology in the foetus is high in the beginning of pregnancy and decreases with increasing gestational age (Dunn *et al*. 1999; Gras *et al*. 2005). Children with congenital *T. gondii* infection may develop recurrent retinochoroiditis later in life; by contrast, individuals infected after birth rarely experience recurrent attacks of retinochoroiditis except when immunocompromised. A study from France of 327 children with confirmed congenital *T. gondii* infection found that 24% (n = 79) had had at least one lesion and 7% (n = 23) had at least one new lesion diagnosed during the follow-up (Wallon *et al*. 2004). It has also been observed that *T. gondii* infections can reactivate during pregnancy in otherwise immunocompetent women (Garweg *et al*. 2005). It is not known why congenitally infected children may experience recurrent attacks of retinochoroiditis. Anergy of T cells to *T. gondii*-specific antigens have been described in a child with congenital toxoplasmosis (McLeod, Beem and Estes, 1985) and a reduced number of circulating CD4+ T cells has been found in newborns with congenital *T. gondii* infection compared to non-infected children (Hohlfeld *et al*. 1990). In another study, children with congenital toxoplasmosis had reduced T cell proliferation and impaired production of IL2 and IFNγ to soluble *T. gondii* antigens compared to those individulals with acquired *T. gondii* infections, demonstrating that congenital infections can impair the specific *T. gondii* cellular immune response (Yamamoto *et al*. 2000). Children with congenital *T. gondii* infections have impaired $\gamma\delta$ and $\alpha\beta$ T cell response. The $\gamma\delta$ T cell response was normalised by the age of one year but the $\alpha\beta$ T cell response was still anergic and the children were not followed further (Hara, 1996). A recent study found an impaired stimulation index to TgGRA1 antigen in children with congenital toxoplasmosis and showed that the relative unresponsiveness improved with age (Guglietta *et al*. 2007).

TRYPANOSOMA CRUZI, CHAGAS DISEASE

In a recent study of children born to *T. cruzi*-infected mothers, 9% (27/302) of newborns were infected (Mora *et al*. 2005) and previous studies have found transmission in between 2% and 12% of children born to women with chronic *T. cruzi* infection (Azogue, la Fuente and Darra, 1985). *Trypanosoma cruzi* infection in the pregnant mother is associated with low Apgar scores, low birth weight, prematurity, respiratory distress syndrome and increased mortality rates in the newborns (Torrico *et al*. 2006). It has been estimated that approximately 1 per 1000 newborns in Argentina in 1993 were congenitally infected with *T. cruzi* (Gürtler, Segura and Cohen, 2003) and the same number has been found in Brazil (Bittencourt, 1992). The outcome of congenital *T. cruzi* infection in the child is not known in detail, but two case reports of congenitally infected siblings both giving birth to congenitally infected children indicate that children congenitally infected with *T. cruzi* can become chronically infected and remain infectious for life (Schenone *et al*. 2001).

Maternal antigens are transferred across the placenta and modulate the foetal immune system. NK cells from newborns with congenital *T. cruzi* infection show an impaired IFNγ production and reduced granzyme B release compared to uninfected newborns (Hermann *et al*. 2006), but develop a fully mature cytotoxic T cell response (Hermann *et al*. 2002).

A study of *T. cruzi*-uninfected newborn children born to *T. cruzi*-infected and uninfected mothers showed that at birth, the newborns born to infected mothers had lower CD3+ and CD4+ T cells but higher numbers of MHC class II co-expression, but at six months of age there was no difference in the markers studied between the two groups of children (Neves *et al*. 1999). Children born to *T. cruzi*-infected mothers showed up-regulation of the pro-inflamatory cytokines IL1β, IL6 and TNFα (Vekemans *et al*. 2000). Whether this protects the newborn child against transmitted *T. cruzi* parasites is not known, but a recent study from Argentina found that children with congenital *T. cruzi* infection were often asymptomatic, although the same study demonstrated second generation transmission from congenitally infected mothers, showing that children with congenital *T. cruzi* infection, although asymptomatic, may remain infective for life (Negrette, Mora and Basombrio, 2005).

FILARIASIS, *ONCHOCERCA VOLVULUS* AND *WUCHERERIA BANCROFTI*

Children born to mothers infected with *O. volvulus* during pregnancy had higher parasite densities when infected with *O. volvulus* later in life and showed detectable parasitaemia at an earlier age compared to children born to mothers without *O. volvulus* infection during pregnancy eighteen years earlier (Kirch *et al*. 2003). Maternal onchocerciasis was a more important risk factor for childhood infection than the *O. volvulus* transmission intensity (Kirch *et al*. 2003). Both Th1 and Th2 cytokine production

is impaired in children born to mothers with *O. volvulus* during pregnancy, which suggest that intrauterine exposure to *O. volvulus* antigens results in hypo-responsiveness (tolerance) to these antigens (Elson *et al.* 1996). Umbilical cord lymphocytes from children born to *O. volvulus*-infected mothers showed a reduced response to *O. volvulus* antigens compared to children born to non-infected mothers (Soboslay *et al.* 1999). A study from Kenya found a Th2- biased immune response and an increased risk of filarial infection in children born to filarial infected mothers (Malhotra *et al.* 2005*b*, 2006).

A study of 21 Polynesian children aged 17 to 19 years showed that children born to mothers who had not had bancroftian filariasis during pregnancy responded to microfilarial antigens but children born to mothers with filariasis during pregnancy had a low IFNγ response (Steel *et al.* 1994). The mechanisms behind the hypo-responsiveness of these children to microfilarial antigens even seventeen years after birth are unclear, but demonstrate that intrauterine antigen exposure can have long-lasting effects on the immune response in the offspring (Clark, 1994). In a family cluster of bancroftian filariasis, children born to infected mothers were more likely to be infected compared to children born to mothers without microfilariasis during pregnancy (Lammie *et al.* 1991).

SCHISTOSOMIASIS

Administration of soluble *Schistosoma mansoni* antigens to pregnant rats results in hypo-reponsiveness to granuloma formation in offspring subsequently infected with *S. mansoni* (Hang, Boros and Warren, 1974). Children born to mothers infected with *Schistosoma mansoni* recognised schistosomal antigens in skin tests and macrophage migration tests, demonstrating that a high proportion of these children had been exposed to *Schistosoma mansoni* antigens during foetal life (Tachon and Borojevic, 1978). Induction of prenatal tolerance to parasite antigens was first demonstrated for schistosomiasis (Lewert and Mandlowitz, 1969) and it has been suggested that early life sensitization will induce tolerance and bias the immune response towards a Th2 answer (Ridg, Fuchs and Matzinger, 1996). Children born to mothers with schistosomiasis or filariasis during pregnancy produced significantly less IFNγ to tuberculin after BCG immunization compared to children born to mothers without schistosomiasis or filariasis during pregnancy (Malhotra *et al.* 1999).

CONGENITAL VIRUS INFECTIONS

Congenital infections with viruses like Rubella, cytomegalovirus and hepatitis B result in a prolonged state of virus excretion and, in the case of hepatitis B, life-long inability to clear the virus. Lessons from these viral infections can be applied to parasitic infections and help to estimate the impact of infections during pregnancy and the perinatal period.

It is well documented in congenital Rubella infections, that the cell mediated immune response is impaired and that this impairment is most pronounced when infection takes place at the beginning of pregnancy and less so towards the end of pregnancy (Buimovici and Cooper, 1985; Ou *et al.* 1993).

Transmission from mother to foetus is also dependent on gestational age in primary, maternal cytomegalovirus, CMV, infection (Stagno *et al.* 1982). However, a study of children with congenital CMV infections found that the CD8+ T cell response was mature and functional (Marchant *et al.* 2003).

The relationship between the risk of developing a life-long, chronic infection and age is particularly well documented for hepatitis B, HBV, infection, and it is estimated that infection at birth will result in chronic infection in 90% of individuals compared to less than 5% in adults over 15 years of age (Lok *et al.* 2001; Ganem and Prince, 2004). The immunological mechanisms in chronic HBV infection are not known in detail, but a role for T-regulatory cells has been proposed (Accapezzato *et al.* 2004). In adults, control of HBV infection relies primarily on cytotoxic T cells and individuals who fail to clear the infection, including neonates and young children, have a reduced early IFNγ response (Hui and Lau, 2005).

CONCLUSION

Data from both protozoan and helminth infections suggest that intrauterine or perinatal exposure to parasites or viruses, either the intact organism itself or soluble antigens transferred across the placenta, reduce the ability of the newborn infant to respond to these antigens, i.e. induce tolerance or anergy (Eynon and Parker, 1993; Nossal, Karvelas and Pulendran, 1993). The results from these studies indicate that a common factor is the reduced ability of T cells and NK cells to secrete IFNγ in response to micro-organism-specific antigens suggesting a bias towards a Th2 response. In malaria, the induced tolerance to malaria antigens results in high parasite densities but also a higher pyrogenic threshold in infants compared to adults. In some studies this hypo-responsiveness was found even two decades after birth, suggesting that the immune modulation by intrauterine antigen exposure may be long lasting and perhaps life-long as is seen for hepatitis B.

Treatment of protozoan and helminth infections in pregnant women should be given priority and studies are needed to determine how the protective immune responses in newborn infants are influenced by treatment of protozoan and helminth infections in the mother during pregnancy.

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