Placental transfer of antibody and its relationship to vaccination in pregnancy

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Abstract

**Purpose of review:** Vaccination in pregnancy boosts maternal vaccine-specific antibody concentration and therefore increases transplacental transfer of antibody to optimise protection of the infant. The purpose of this review is to describe what is known about placental transfer of antibody in the context of vaccination in pregnancy, focussing on the recent literature and areas of debate, particularly about the timing of vaccination.

**Recent findings:** There is debate about the timing of pertussis vaccination in pregnancy with some studies reporting that vaccination in the third trimester results in higher pertussis antigen specific IgG concentrations in cord blood and others finding that the concentration is higher following vaccination in the second trimester. The impact of timing of vaccination on antibody avidity in cord blood has also been investigated and one study suggests that avidity may be increased following vaccination at 27 - 30+6 gestational weeks compared to later vaccination.

**Summary:** Understanding placental transfer of antibody is vital in informing maternal vaccination strategy. There has been recent research about the timing of pertussis vaccination in pregnancy which has implications for the timing of both current and future vaccines to be used in pregnancy.

**Key words:** Placental transfer, IgG, vaccination, neonatal Fc receptor

Introduction

At birth human infants are immunologically immature and protective immunity against the wide range of pathogens they are exposed to *ex utero* depends in large part on the transfer of humoral immunity from mother to infant. It has been known for over one hundred years that this immune transfer takes place and we now have a much clearer idea about the specific mechanisms by which this occurs. Vaccinating women during pregnancy is a strategy which seeks to increase the protection of mother, fetus and infant by boosting concentrations of specific antibody in the mother and consequently the amount available for transplacental transfer. This is particularly important for the period of increased susceptibility to infection from birth until such time as the infant is protected by infant immunisation or the period of greatest risk has passed. The extent to which vaccination in pregnancy can offer protection to the newborn infant is largely dependent on the degree of placental transfer possible for pathogen specific IgG.

**Placental structure**

The placenta is a vascular organ of which the basic functional units are the chorionic villi. These allow close association of the maternal and fetal circulations with the placental membrane acting as a barrier between them. There is now good evidence that transplacental transfer of antibody is facilitated by the neonatal Fc receptor, FcRn, which is expressed in the human syncytiotrophoblast. [1]

**Transfer of immunoglobulin subclasses**

IgG is the only immunoglobulin which is transported across the placental barrier and the subclasses of IgG demonstrate variable affinity for the FcRn receptor leading to differences in the efficiency of transfer. The greatest transport efficiency is for IgG1, followed by IgG4, IgG3 and finally IgG2. [2] This differential ability of immunoglobulin to be transferred is important in the context of vaccination in pregnancy as exposure to a protein antigen tends to induce an IgG1 response with smaller amounts of IgG3 and IgG4, and a polysaccharide antigen tends towards a predominance of IgG2 with some IgG1. [3]

**Timing of antibody transfer**

There is minimal placental transfer until around 13-16 gestational weeks (GW) with the fetal level of IgG before 16 GW being <8% of adult level.[4] Following this, there is a continuous increase throughout the second trimester with a sharper increase in the third trimester [2] and a large amount of transfer in the last four weeks [2,4] leading to levels in the fetus often exceeding maternal levels at delivery.[5] This increase in placental transfer is not entirely understood, but it has been suggested that in the first months of gestation the cytotrophoblast may obstruct transfer, leading to improved transfer as this layer degrades. [6] Another hypothesis is that the FcRn receptor is more highly expressed with advancing gestation [7], which would explain the increasing placental transfer as gestation advances. This clearly has implications for preterm infants as not only do they have a reduced period of gestation in which placental transfer can occur, but placental transfer is also less efficient earlier. They can however still benefit from vaccination in pregnancy with a recent study showing that premature infants born at 28-35 GW to mothers vaccinated in pregnancy with Tdap/IPV vaccine from 28 GW had significantly higher antibody concentrations at 2 months of age for all measured vaccine antigens compared to those infants born at the same gestation to unvaccinated mothers. [8] This increase in efficiency of antibody transfer is important when making decisions about timing of vaccination in pregnancy particularly where vaccination in pregnancy is for the protection of the infant following delivery, for example pertussis vaccination, rather than primarily to reduce the risks to the woman or fetus during pregnancy as in the case of influenza vaccination.

**Timing of vaccination in pregnancy**

Pertussis vaccination in pregnancy has been introduced in many high income countries in recent years, including the UK in 2012. These antenatal vaccination programmes were introduced as a response to the significant increase in reported pertussis cases across all age groups, but particularly in young infants, for whom disease is most severe and who are too young to be protected by the infant vaccination programme. Of particular concern was the number of infant deaths attributable to pertussis. [9] This strategy has been shown to be effective in preventing cases of pertussis in infants. [10-12]

 In many countries the vaccine was initially recommended after 26-28 GW based on the relatively short half-life of the pertussis antibody following vaccination [13], the increasing efficiency of placental transfer as gestation advances and the need to allow time following vaccination for the antibody to be transferred to the fetus before delivery.

There remains debate in the published literature about the optimal timing of pertussis vaccination in pregnancy in order to ensure optimal benefit to the infant. Healy et al enrolled 105 women who had delivered an infant at >37 GW and had received a Tdap vaccination within the previous 2 years, 19 of whom received the vaccination during pregnancy. The authors calculated that only 40% of infants had a PT-specific IgG concentration at birth calculated to remain above the lower limit of quantitation (LLOQ) of the assay at two months. They found that slightly more infants of mothers immunised during pregnancy and 2 of the 3 women immunised after 20 GW had PT levels at birth which would persist above the LLOQ until 2 months. Based on their findings they recommended vaccination at 30-32 weeks to coincide the highest levels of antibody with the time of maximal placental transfer. [14] In a recent study looking at vaccine effectiveness (VE), with the primary outcome of interest being pertussis in the infant at <8 weeks of age, it was shown that vaccination between 27-36 GW is more effective in preventing pertussis in infants <8 weeks of age compared to vaccination given at any point in pregnancy. In a subanalysis of results from mother-infant pairs who received Tdap during pregnancy and >14 days prior to delivery it was shown that infants whose mothers were vaccinated in the second trimester were significantly more likely to have pertussis at <8 weeks (OR 8.1, 95% CI 1.3-49). These findings led the authors to recommend vaccination between 27-36 GW. [15]

In contrast, other studies have suggested that earlier vaccination may be preferable. Naidu et al found that vaccination between 28-32 weeks’ gestation compared to vaccination between 33-36 GW led to significantly higher levels of Pertussis Toxin (PT) (4.18 vs 3.50 IU/ml, p=0.009), Filamentous Haemagglutinin (FHA) (5.56 vs 5.03 IU/ml, p=0.03) and Pertactin (PRN) (5.83 vs 5.31IU/ml, p=0.03) in cord blood. However, when adjusting for pre-vaccination maternal antibody levels, the comparison only remained significant for PRN (p=0.03). [16] Abu Raya et al had similar findings in their study of 61 women vaccinated between 23 and 38 weeks’ gestation. Cord geometric mean concentration (GMC) of IgG to PT and FHA were significantly higher in infants of women vaccinated at 27-30+6 GW (PT 46.04 IU/ml 95% CI 24.29-87.30, FHA 225.86 IU/ml 95% CI 182.34-279.76) compared those vaccinated at 31-36 GW (PT 8.69 IU/ml 95% CI 3.66-20.63 FHA 178.31 IU/ml 95% CI 134.59-237.03) or >36 GW (PT 21.12 IU/ml 95% CI 7.93-56.22 FHA 138.03 IU/ml 95% CI 97.61-195.16). [17]

There is now some evidence that perhaps even earlier vaccination may be desirable. In an observational study of 335 women who had received vaccination from 13 GW 122 women received second trimester vaccination and 213 third trimester vaccination. Anti-PT and FHA GMCs in cord blood were significantly higher following second vs third trimester immunization (PT: 57.1 EU/ml 95% CI, 47.8-68.2 vs 31.1 EU/ml 95% CI 25.7-37.7, p<0.001. FHA: 284.4 EU/ml 95% CI 241.3-335.2 vs 140.2 EU/ml 95% CI 115.3-170.3, p<0.001) with expected infant anti-PT antibody levels of >5EU/ml in 98% and 86% of infants born to mothers vaccinated in the second and third trimester respectively. [18] There is some debate about the mechanism behind this, [19, 20] but the authors suggest that the most important reason may be the longer cumulative exposure following early vaccination.

In another study, of women vaccinated from 20-36 GW there was no relationship seen between time of vaccination and antibody levels in cord blood at delivery with IgG anti-PT levels >10IU/ml being found in 93.6%, 95.2%, 95.5% and 95% of neonates born to mothers vaccinated at 20-23, 24-27, 28-31, 32-35 GW respectively. [21] In another study, the timing of antenatal vaccination was not associated with any of the infant pre-immunisation antibody concentrations or proportions achieving protective thresholds for the antigens in the maternal vaccine except for FHA where the authors observed a 1.08- fold increase (95% CI, 1.03-1.14) was observed per week prebirth (p=0.002). [22]

Antibody avidity

There is evidence that increasing antibody avidity is associated with increasing serum bactericidal activity against specific pathogens [23, 24] and avidity may also play a role in the efficiency of antibody transfer across the placenta with placental transfer possibly being more efficient for high avidity antibodies. [25] In one study looking at pertussis vaccination, the investigators found that newborns of women immunised from 27-30+6 had higher relative avidity index (RAI) than those of mothers vaccinated later. [26] There is some debate about this however and another group have found that the gestation at vaccination had no impact on the antibody avidity in the infant. [27] This is an area which requires further exploration, both in terms of the impact of avidity on placental transfer and the impact of timing on avidity.

Different antigens

Antibody produced against different antigens are variably transferred across the placental barrier. In a study in China it was shown that measles antibody had more efficient placental transfer than antibody to HIV, poliovirus or coxsackie virus. [28] A UK study which included both HIV infected and uninfected mothers showed that pertussis and tetanus antibody were transferred more efficiently than Hib antibody in both groups [29] This differential transfer with different antigens could be explained by the different proportions of IgG subclasses produced after exposure to different antigens [30].

Reduced placental transfer

Antibody levels in the mother are important for the transfer of antibody to the fetus, with higher levels of pathogen specific antibody being associated with higher levels in the newborn. Placental transfer can be reduced however when the total amount of antibody in the mother is very high, as the FcRn receptor becomes saturated. [7] This reduces the transfer ratio, although the absolute amount transferred may still remain high. A recent study looking at transplacental transfer of maternal RSV antibody found that hypergammaglobulinaemia was independently associated with reduced transport ratio and that this reduction was most pronounced in mothers with the lowest titres of RSV-specific neutralising antibody. [31]

Specific conditions affecting placental transfer: Human Immunodeficiency Virus (HIV) and malaria

Malaria and HIV have both been implicated in reduced transplacental transfer of antibody, but there is significant heterogeneity in the findings from different studies.

HIV infection in the mother has been shown to reduce the transplacental transfer of antibodies against a range of pathogens including tetanus, GBS, VZV, measles, Hib, pertussis and pneumococcus [29, 31-39] in many studies, although this is not a universal finding. Importantly, many of these studies showed that not only was transplacental transfer reduced, but also neonates were more likely to be seronegative for specific pathogens compared to infants born to HIV negative mothers. Compounding the impact of reduced transplacental transport is that HIV positive women often have lower disease specific antibody levels which renders these infants uniquely susceptible to disease. Vaccination in pregnancy could be particularly useful in improving the immunity of these infants as although the vaccines may have reduced immunogenicity in HIV infected women, because they and their infants are at particular risk of infection even a small increase in immunity can be beneficial. A recent study of a GBS vaccine showed that the vaccine was less immunogenic in HIV infected women, although interestingly there was no impact of HIV infection in transplacental transfer ratio. [40] Another recent study has shown for GBS that whilst placental transfer of total IgG was reduced in HIV infected women for GBS serotypes (ST) I and III and IgG1 was reduced for GBS STIII, placental transfer of IgG2 for all serotypes studied was unaffected by HIV status. [41]

Malaria has been shown to reduce transplacental transfer of antibody against tetanus, measles, *S. pneumoniae*, HSV-1, RSV and VZV in some studies [33, 37, 42-44], but other studies have shown no impact on transplacental transfer of tetanus, *S. pneumoniae*, Hib, diphtheria toxoid or RSV antibody. [31, 37, 43] The variation in findings may be due to difference in the study population, the lab techniques used and the women and infants included in the study, particularly in the parameters set regarding gestation at delivery. A recent study suggests that the previous findings of a reduction in transplacental transfer of specific antibody in the context of placental malaria may be due to confounding factors, for example the impact of prematurity and hypergammaglobulinaemia. [31, 45]

Discussion

Vaccination in pregnancy offers the opportunity to provide protection to immunologically immature infants at a time of increased vulnerability before they can receive their own vaccinations. Our ability to offer effective vaccine programmes in pregnancy relies on us having a good understanding of the immunobiology of placental transfer so that we can direct future work more specifically. As we have seen in the case of pertussis, there remains uncertainty about the timing which would afford the best protection to newborns and this is an area which requires future work as it may be relevant not only for pertussis, but also for other maternal vaccines. This issue is particularly important for premature infants because of their increased vulnerability. Another important area for future work is to further consider the limitations to placental transfer and particularly what steps might be taken to overcome this. Although there is some variability between studies, high overall levels of immunoglobulin as well as HIV and placental malaria have all been associated with reduced efficiency of placental transfer. As these conditions are prevalent in low income settings in which morbidity and mortality from infectious diseases are highest they represent an area of priority.

Placental transfer of antibody is a vital area to explore when considering vaccination in pregnancy, but it is not the only one. Maternal level of antibody is also important and additionally there are practical issues to be considered, for example, infrastructure, seasonal availability of some vaccines and public opinion about vaccination in pregnancy. This latter area is particularly relevant for this review as it may be that timing of vaccination in pregnancy needs to be considered in the light of both evidence of the best transfer of immunity and public acceptability. In a literature review about factors contributing to vaccine hesitancy published in 2015, the authors report that the main concern related to safety [46] and concern about vaccination in pregnancy often centres on concerns about complications for the developing fetus. For this reason it may at times be pragmatic to recommend vaccination following the anomaly scan at 20 GW even when earlier vaccination has been shown to allow good transfer of immunity.

Conclusions:

Vaccination in pregnancy is already used very effectively for tetanus, influenza and pertussis and has the potential to protect women and their infants against other pathogens in the future. We need to understand the mechanisms behind placental transfer of antibody, and the factors which limit this process, so that vaccine programmes can be designed to provide optimal protection.

Key points:

1. Placental transfer of antibody is vital in providing immunity to the newborn and is facilitated by the neonatal Fc receptor, FcRn found on the syncytiotrophoblast of the placenta
2. Placental transfer increases through the pregnancy and the efficiency of transfer is dependent on a number of factors
3. The optimal timing of pertussis vaccination in pregnancy is still not known with a range of findings in studies: some showing increased antibody concentration in the cord after vaccination in the second trimester, some after vaccinaton in the third trimester and some studies showing that timing of vaccination is not important in neonatal immunity.
4. Avidity may be important in the transplacental transfer of antibody and this area requires further work.

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