Antibody glycosylation in pregnancy and in newborns: biological roles and implications

Thomas F Rice[1], Beth Holder[1] and Beate Kampmann[2,3,4]

[1]Department of Metabolism, Development and Reproduction, Imperial College London, UK

[2]Section of Paediatrics, Department of Medicine, Imperial College London, UK

[3]The Vaccine Centre, London School of Hygiene and Tropical Medicine, UK

[4]Vaccines & Immunity Theme, MRC Unit The Gambia at LSHTM, The Gambia

Corresponding author:

Beate Kampmann

Professor of Paediatric Infection & Immunity

Director, The Vaccine Centre

London School of Hygiene and Tropical Medicine

Theme Leader Vaccines & Immunity

MRC Unit The Gambia @ LSHTM

E: beate.kampmann@lshtm.ac.uk

bkampmann@mrc.gm

T: +44 20 7 612 7925

A: Faculty of Infectious & Tropical Diseases| Room 367| Keppel Street

London WC1E 7HT

Abstract

Purpose of review: Glycosylation patterns have the potential to affect the function of antibody, antibody half-life and transplacental transfer from mother to fetus. Here we review recent advances in our understanding of how glycosylation patterns of antibodies may be altered during pregnancy, vaccination and infection.

Recent findings: During pregnancy, there is preferential transplacental transfer of NK cell-activating antibodies that are galactosylated and sialylated, against both bacterial and viral antigens. Markers of NK cell function are also associated with a higher abundance of galactosylation and sialylation in respiratory syncytial virus-specific IgG, compared to total IgG, in infants up to seven months of age which may suggest a role for NK cell-activating antibodies as important mediators of immunity during early infancy. Differential glycosylation patterns have been observed in some respiratory conditions, as increased non-galactosylated antibodies have been associated with the development of chronic inflammatory bronchopulmonary dysplasia (BPD) in preterm infants. Glycosylation patterns in children appear age-dependent, which could modulate the effector function of IgG. The clinical relevance of these findings needs to be established.

Summary: Glycosylation plays a key role in mediating antibody function. Glycosylation patterns associated with positive outcomes from infection in mothers and infants could inform the design of the next generation of vaccines for use in pregnancy and infancy.

Key words: glycosylation, antibody, pregnancy

Introduction

Glycosylation is the process through which glycans, or polysaccharides, are added to proteins. In the case of antibody, or immunoglobulins (IgG), this addition occurs at the fragment crystallisable (Fc) region. The Fc region (**Figure 1**) is the antibody tail that enables the interaction of antibody with cell surface Fc receptors, found on many types of immune cells, including natural killer (NK) cells, macrophages and neutrophils. Biantennary 2 n-acetylglucosamine (GlcNAc) and mannose residues make up the core glycan and different glycosylation patterns can be determined by the addition of a bisecting GlcNAc, galactoses, sialic acids or fucose. Glycosylation patterns of the Fc region are affected by age,[1] sex,[2] pregnancy,[3] infection and vaccination,[4,5] which in turn impacts antibody function, half-life and transfer.[6,7] IgG is involved in the adaptive immune response against a number of infections, and therefore changes in the glycan structure at the Fc region affect an individual's susceptibility to infection and disease severity.[8] Pregnancy and the neonatal period both represent key immunological periods in the life-course; including maternal immunomodulation during pregnancy, maternal and neonatal vaccine administration, and neonatal exposure to new pathogens. The aim of this short review is to evaluate recent antibody glycosylation studies in both animal models and humans and its relevance to pregnant women, neonates and infants.

Laying the Foundations: Antibody glycosylation in pregnancy and transfer to the fetus *in utero*

Pregnancy is a period of dynamic immune modulation, with changes observed in both circulating and local immune cell subsets across gestation. In the periphery, this includes T helper cell cytokine responses, the proportion of asymmetric antibodies and antibody glycosylation.[3,9] During pregnancy, IgG antibodies are transported across the placenta to the fetus, helping to provide protection against diseases in the neonatal period.[10] Taking advantage of this are several existing and under-development maternal vaccines, aimed at boosting protective IgG levels in the infant through administration in pregnancy. Transfer of maternal IgG across the placenta is mediated by binding to receptors such as the neonatal Fc receptor, FcRn, and may involve other receptors such as Fc fragment of IgG, low affinity IIIa, receptor (FCGR3A). As these receptors bind to IgG through the Fc region, glycosylation affects IgG-receptor affinity. Changes in IgG glycosylation during pregnancy may therefore not only be important for maternal responses to infection and vaccination, but could also affect disease susceptibility in the infant, either through altering the quality of antibodies produced by pregnant women in response to vaccination or by affecting antibody transfer through the placenta through modulation of FcR-IgG interactions.

Systems serology aims to comprehensively survey a diverse array of antibody features and functions to identify antibody features required for protection. Jennewein *et al*. 2019[11] utilised this approach to investigate whether patterns of antibody glycosylation impacted on antibody transfer during pregnancy, using paired maternal and cord samples as a proxy of placental transfer efficiency. In serum samples from women vaccinated against *Bordetella pertussis* during their pregnancy, they demonstrated preferential transplacental transfer of NK cell-activating IgG antibodies against pertussis antigens: compared to pertussis-specific maternal antibodies, cord antibodies had increased proportions of CD107a+, IFN-γ+ and MIP-1β+ NK

cells.[11] The authors confirmed that this observation also extended to antibodies against respiratory syncytial virus, influenza and measles.[11]

The authors proposed that the increased transfer of antibodies involved in NK cell activation to neonates was due to preferential placental transfer of antibodies with specific functional properties from mother to the fetus. They demonstrated a preference for the enhanced transfer of galactosylated and sialylated antibodies across bulk and antigen-specific antibody populations, and that digalactosylated antibody interacted effectively with neonatal Fc receptor FcRn and FCGR3A, and therefore may be selectively captured and transferred.[11] The preferential transfer of NK cell-activating antibodies suggests that these antibodies are important in providing protection to the neonate in the first few weeks of life, and that NK cells may play a pivotal early role in the neonatal immune response to infection. This suggests that NK cell-activating antibodies might be important in the protection against a variety of diseases, and this might be considered when designing vaccines to be used in pregnancy and in infants in early life.

A limitation of this study is that the authors combined maternal and cord blood data from Tdap-vaccinated and unvaccinated pregnancies, as their evaluation of total and antigen-specific antibody profiles found no difference between mothers from Tdap-vaccinated and unvaccinated pregnancies. This is surprising, as all other studies unequivocally show that Tdap-vaccination during pregnancy boosts vaccine-specific antibody levels in both pregnant women and their infants.[12–20] The results therefore suggest that the systems serology platform utilised in this study was not able to detect Tdap vaccine-specific responses in pregnancy, unlike the approaches used by previous studies comparing antibody titres between vaccinated and unvaccinated groups.

Maternal HIV infection during pregnancy is associated with neonatal morbidity and impaired vaccine responses in the absence of vertical transmission. Martinez *et al*. 2019[21] assessed the placental transfer of pathogen-specific IgG in two cohorts of HIV-infected women, one from Malawi and one from the United States. The authors report wide variability in the transfer of antigen-specific IgG and split the subjects into groups based on transfer efficiencies of IgG from mother to fetus categorised as: efficient, variable or poor. Assessing the transfer of antibody levels to the HIV-glycoprotein antigen gp120 and also to antibodies to common pathogens such as tetanus toxoid and pertussis toxin, differences in Fc region glycan profiles were demonstrated within the designated transfer groups. For example, in HIV-infected women with variable transfer efficiency, poorly transferred gp120-specific IgG had higher frequencies of Fc region fucose.[21] This is in contrast to tetanus toxoid and pertussis toxin, which had overall lower levels of fucose and were efficiently transferred. The authors therefore propose that Fc region glycans may modulate the selective transfer of IgG subpopulations. The limitation of this study is that the groups used for the statistical analysis were created post-hoc, with arbitrary definitions of 'efficient' and 'poor' transporters making it difficult to interpret the findings and their clinical relevance, or apply to other study populations. Most importantly, the impact of maternal HIV infection on the transfer efficiency of antigen-specific IgG and the role of Fc region glycosylation in transfer efficiencies remains to be determined, as this study did not include an HIV-negative control group. The specific impact of HIV on glycosylation patterns or indeed other co-infections warrants further investigation. In addition, and acknowledged by the authors, maternal genetic and environmental differences exist between the cohorts from Malawi and the United States, which may be why factors associated with placental IgG transfer efficiency did not always correlate between cohorts. Despite these limitations, the authors demonstrate that placental transfer of maternal IgG is a selective process, determined by a combination of factors including antibody subclass and glycan profiles.

Recent epidemics of Zika virus (ZIKV) have occurred in French Polynesia and South America. ZIKV infection in early pregnancy is associated with severe birth defects, primarily microcephaly, and there is an urgent need for a preventive vaccine. Frumence *et al*. 2019[22] inoculated mice with an engineered non-glycosylated Zika virus. They observed that immune sera from these mice failed to neutralize strains from epidemics in French Polynesia and Brazil. The authors suggest that the changes in glycosylation patterns on the virus impacted the accessibility of neutralizing antibody epitopes on mature virus particles, something that will have important implications in in the development of effective vaccines against ZIKV.

Time zero: antibody glycosylation at birth

Non-galactosylated glycans have been associated with inflammation-mediated immune diseases.[6] The amount of antibody transferred to the fetus increases with gestational age and therefore pre-term infants may be at higher risk of infection due to the lower levels of total IgG they are born with.[23] Twisselmann and colleagues evaluated glycosylation patterns in infants grouped by gestation of birth: extremely preterm (born < 28 weeks of gestation), preterm infants (born ≥28 and ≤ 35 weeks of gestation) and term infants (>36 weeks).[24] They observed that the proportion of sialylated IgG Fc glycans was reduced in the extremely low gestational age group, compared to preterm and term infants. This effect was also observed for bisecting glycans, when comparing infants from the two preterm groups. An increased proportion of non-galactosylated glycans were found in the extremely low gestational age infants, compared to preterm and term infants.[24] The authors then assessed whether there were correlations between IgG Fc glycosylation and the clinical characteristics of the preterm infants in the study. Whilst there was no significant relationship between Fc glycosylation patterns and sepsis, an increase in non-galactosylation was associated with the development of chronic inflammatory bronchopulmonary dysplasia (BPD) in preterm infant's ≥28 week's gestation.[24] Conversely, galactosylation was associated with reduced BPD in this group. These effect were not observed

in pre-term infants born <28 weeks of gestation. Whilst the BPD group in this study was small, these findings do suggest that non-galactosylated glycans with pro-inflammatory effects may contribute to inflammatory disease. However, further study is required to determine whether the increase in non-galactosylation in preterm infants is a cause or an effect of diseases such as BPD.

Some vaccines, such as Bacillus Calmette–Guérin (BCG), can be given at birth. As well as protecting against *Mycobacterium tuberculosis*, the vaccine has been associated with a reduction in all-cause mortality, which has been suggested to be linked through reprogramming of the neonatal immune system. The host response to *M. tuberculosis* plays a major role in the determination of the different clinical manifestations of the disease and therefore changes in the glycosylation status of antibody may reflect the disease status of the host. Although defence against *M. tuberculosis* is primarily mediated by cellular immune responses, changes in antibody glycosylation patterns are observed between *M. tuberculosis*-infected and naive mice, in the presence and absence of BCG vaccination.[4] Naïve mice infected with *M. tuberculosis* have increased glycan fucosylation of IgM, suggesting that infection itself alters glycan processing. Interestingly, the elevation in fucosylation in response to *M. tuberculosis* infection was blunted in mice that had received the BCG vaccine.[4] Removal of fucose has been associated with changes in antibody function, most notably the enhancement of antibody-dependent cellular cytotoxicity.[6] The blunting of the fucose response in BCG-vaccinated mice may represent a mechanism by which the vaccine is able to contribute to protective immunity and the vaccine's known heterologous effects. This may have important implications in countries in which the BCG vaccine is given at birth, but further study is required to determine if these findings can be replicated in humans.

Growing with glycans: antibody glycosylation in infancy

Differential glycosylation patterns have been observed in a study of infant respiratory syncytial virus (RSV).[25] Blood samples from a cohort of infants less than 7 months of age had higher abundance of galactosylation and sialylation in RSV-specific IgG, compared to total IgG. Age-dependent differences were also noted, with increased fucosylation of both RSV-specific and total IgG with age, but decreases in galactosylation, sialylation, and bisecting glycans.[25] These findings demonstrate age-dependent changes in Fc glycans on both total and antigen-specific antibodies, suggesting pan-IgG regulation of glycosylation with age.

This study also found correlations between RSV-specific IgG Fc glycosylation and markers of NK cell function. Although in some cases the correlation was small, the expression of IFN-γ and CD107a on NK cells was negatively associated with fucosylation, but positively associated with sialylation and galactosylation. Like the study of antibody transfer from mother to fetus by Jennewein *et al*. 2019[11], a link between glycosylation and NK cell function was demonstrated. Importantly, these effects were confirmed to be present in infants in later life, suggesting NK cell-activating antibodies are important mediators of immunity during the neonatal period.

Age-dependent differences in glycosylation patterns have been previously demonstrated.[1,6] In a cross sectional study, de Haan and colleagues found increased fucosylation in early childhood (0.1-3.9 years), compared with infants at birth. In contrast, galactosylation, sialylation and bisection decreased with age.[26] Cheng *et al*. 2019[27] also found that age-dependent glycosylation patterns were evident across different subclasses of IgG. In this study, children were categorised by age: 9 months to 2 years, 2 to 5 years and 5 to 18 years. Whereas the levels of monogalactosylated and bisected IgG increased with age, there were decreases in levels of digalactosylation, sialylation and fucosylation in older children.[27] This suggests that

glycosylation patterns are age-dependent, which could modulate the effector function of IgG in older children.

Cheng *et al*. 2019[27] also hypothesised that changes in patterns of IgG Fc glycosylation may be a contributing factor to unexplained recurrent respiratory infections (RRI). Interestingly, the levels of bisected glycans were elevated in the RRI group, compared to age-matched healthy children, and this was consistent across all subclasses. In addition, sialylation was increased on the IgG2/3 and IgG4 subclasses.[27] However, much like the study of Twisselmann *et al*. 2019[24], the question remains whether the differences in glycosylation patterns are a cause or an effect of infection.

As IgG glycan structures can influence effector functions, their role in predicting disease susceptibility or severity is becoming increasingly important. In a study of paediatric meningococcal sepsis, de Haan *et al*. 2018[8] investigated the hypothesis that IgG Fc glycosylation might be related to the susceptibility and severity of meningococcal sepsis. Addressing the question of susceptibility, the authors observed that Fc fucosylation of IgG1 was decreased in meningococcal sepsis patients, compared to a cohort of age-matched healthy controls. Interestingly, when splitting the cohorts by age (0 to 3.9 years versus 4 to 18 years), this effect was more pronounced in patients less than 4 years of age.[8] In a reversal of the pattern seen for fucosylation, IgG1 Fc bisection was elevated in meningococcal sepsis patients, compared to the healthy group. Future studies of this type could assess whether these glycosylation patterns are similar to those of healthy children, following recovery from meningococcal sepsis, an important question to distinguish between cause and effect.

Assessing how glycosylation might be related to the *severity* of meningococcal sepsis, de Haan and colleagues observed lower levels of IgG1 hybrid type glycans and IgG2/3 sialylation per galactose in infants that later required amputation or died, compared to those that did not.[8] This

could be because severe meningococcal infection induces a change in IgG glycosylation, or that infected children who produce these type of IgGs are at higher risk of developing severe disease. Access to both convalescent and pre-infection samples would help to address this question. The potential to use changes in glycosylation as a biomarker for identifying children susceptible to infection is attractive, and future research should focus on whether these differences are present on meningococcus-specific IgG compared to total IgG.

Conclusions

Glycosylation plays a key role in mediating antibody function, half-life and transfer. It still remains to be established how much antibody glycosylation contributes to clinically relevant differences in functionality with regards to disease outcomes or vaccine responses in pregnancy and the neonatal period. If such clinical relevance can be demonstrated, the assessment of glycan patterns could be used as biomarkers to predict immune responses to infection in neonates and/or maximise vaccine-induced responses. The studies highlighted and discussed in this review suggest that a move towards this type of measurement may help to identify individuals that are more susceptible to infection or to their severe outcomes. In the field of precision medicine, such results could inform the clinical management of patients, and glycan profiling represents an exciting avenue to pursue this. In addition, the discovery of glycosylation patterns associated with positive outcomes from infection in mothers and infants could inform the design of the next generation of maternal and paediatric vaccines. The impact of factors such as age, gender and geographical location on healthy individuals must also be considered to further understand the baseline of antibody functionality mediated by glycosylation, and to be able to interpret infection- and vaccine-induced responses in this context.

Increasingly, therapeutic antibodies are being designed for use in oncology, autoimmune and inflammatory-mediated diseases. There is also potential for their use to improve the health of mothers and infants. For example, glycosylation patterns influence the half-life of antibodies, and the extension of the half-life of antibody generated through maternal vaccination may provide longer-term protection to neonates. In addition, the strength of binding of antibody to placental FcRn may be improved by designing antibodies with alternative glycosylation patterns, improving the transfer of antibody from mother to fetus.

Key points

- Glycosylation patterns determine the type of antibody that is preferentially transferred from mothers to the fetus during pregnancy, with a preference for NK cell-activating antibodies.
- The importance of glycosylated NK cell-activating antibodies has also been observed in infants infected with RSV
- Glycosylation patterns in infants are age-dependent and may predict susceptibility or severity of disease
- Glycosylation patterns could inform the design of the next generation of maternal and paediatric vaccines, however, whether observed patterns are a cause or effect of infection remains to be established

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Conflicts of interest

None

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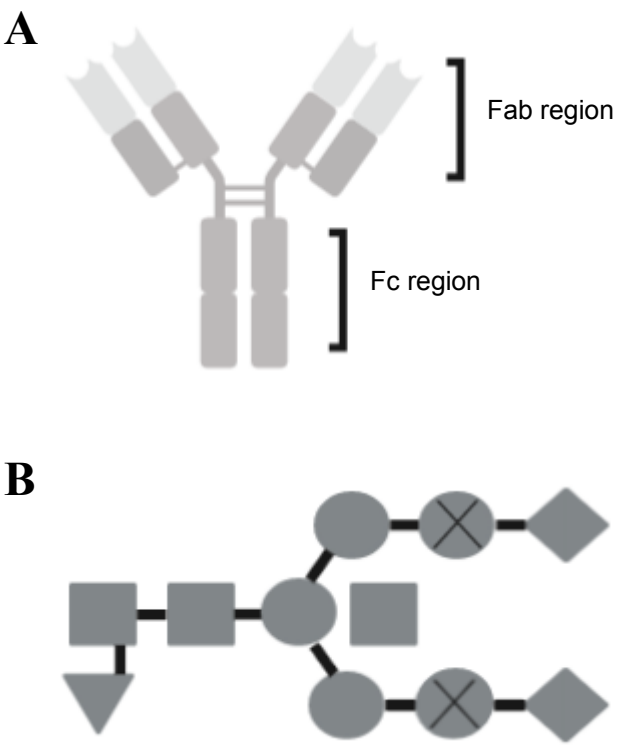

Figure 1. Glycosylation of antibodies. A) Glycosylation occurs at the Fc region of IgG B) Biantennary GlcNAc (2 n-acetylglucosamine; squares) and mannose residues (circles) make up the core glycan. Antibody effector function can be determined by the addition of a bisecting GlcNAc, galactoses (circle with cross), sialic acids (diamond) or fucose (triangle).