3

Transplacental transport of IgG antibodies to preterm infants: A review of the literature

Jolice P van den Berg, Elisabeth AM Westerbeek, Fiona RM van der Klis, Guy AM Berbers, Ruurd M van Elburg

Early Human Development 2013 Feb;87(2):67-72

Abstract

Background Newborn infants, especially preterm infants, have an immature immune system, which is not capable to actively protect against vaccine-preventable infections. Therefore, the newborn is dependent on transplacental transport of Immunoglobulin G (IgG), an active, FcRn receptor mediated process. Fetal IgG rises from approximately 10% of the maternal concentration at 17-22 weeks of gestation to 50% at 28-32 weeks of gestation. If transplacental acquired IgG is lower in preterm than in term infants, preterm infants are especially at risk for these vaccine preventable diseases.

The aim of this study was to review the transplacental transfer of IgG against vaccine-preventable diseases (measles, rubella, varicella-zoster, mumps, Haemophilus influenza type B, diphtheria, tetanus, pertussis and polio) to (pre)term infants and to identify factors that influence the transplacental transfer of these antigens.

Methods After selection, 18 studies on transplacental transport to preterm infants were included.

Results In general, these studies showed for all antibodies that preterm infants have lower antibody concentrations infants compared with term infants. Maternal and infants antibody concentrations showed a strong correlation in 7 of the included studies. Infant antibody concentration was not associated with parity, maternal age, height or weight. Infants of vaccinated mothers had lower anti-measles antibody titers than infants of natural immunized mothers. IgG titers of preterm infants decrease earlier in life below protective antibody titers than term infants. Combined with their immature immune system, this puts preterm infants at increased risk for vaccine-preventable diseases.

Introduction

Newborn infants, especially preterm infants, have an immature immune system, which is not capable to actively protect against vaccine-preventable infections like diphtheria, tetanus, pertussis, measles, mumps, rubella, *Haemophilus influenzae* type B and Neisseria meningitidis C.[32-34] Maternal Immunoglobulin G (IgG) is transported over the placenta (transplacental transport) by an active, FcRn receptor mediated process during pregnancy and protects (pre)term infants against the different infections during the first months of life.[25]

In 1967, Hobbs et al found an exponential relationship between total IgG and gestational age (GA) in preterm infants.[76] In the first trimester, very little IgG is transported to the fetus.[29,30] In the second trimester, the fetal IgG rises from approximately 10% of the maternal concentration at 17-22 weeks of gestation to 50% at 28-32 weeks of gestation as determined by chordocentesis. [25,31] In the third trimester, the increase of fetal IgG concentration between 29 and 41 weeks of gestation is two times as high as between 17 and 28 weeks of gestation.[30] The concentrations of the IgG subclasses in the fetus are not equally distributed,[77] because IgG1 and IgG4 are transported more efficiently than IgG3, and IgG2 is transported the least efficiently.[78] This is caused by different affinity for FcY receptors.[79] Therefore, transplacental transport of antibodies of vaccine components differs between the elicited types of IgG antibodies, as polysaccharides vaccines (like MenC and Hib) elicit mainly IgG2 antibodies,[80,81] whereas protein vaccines (like diphteria, tetanus, pertussis) elicit more IgG1 and IgG3 antibodies.[82,83] In general, higher IgG levels at birth are thought to be associated with better and longer protection and until the first vaccinations are administered, transplacental transported maternal IgG is the main humoral protectin against vaccine-preventable diseases for infants, adjusted with herd immunity in vaccination areas. We hypothesize that preterm infants have lower amounts of transplacental acquired IgG than term infants, which poses them especially at risk for these vaccine preventable diseases. Beside GA, other factors, such as birth weight (BW), age of the mother or parity may influence transplacental transport of IgG. Increased insight in the factors involved in transplacental transport of IgG may help to identify infants at risk for vaccine preventable infections and to develop strategies to decrease these risks in (pre)term infants.

Therefore, the aim of this study was to review the literature on transplacental transfer of IgG, against measles, rubella, varicella-zoster, mumps, *Haemophilus influenza* type B, diphtheria, pertussis, tetanus and polio especially in preterm infants and to identify factors that influence the transplacental transfer of these antigens.

Methods

A literature search was performed in Pubmed including articles published until February 2010.

Key words and limits were: (("gamma-Globulins"[Mesh] OR "Immunoglobulin G"[Mesh]) AND ("Infant, Premature"[Mesh])) OR (("Antibody Formation"[Mesh]) AND ("Infant, Premature"[Mesh])) OR ((("Maternal-Fetal Exchange"[Mesh]) OR ("Immunity, Maternally-Acquired"[Mesh])) AND ("Infant, Premature"[Mesh])) OR (("Antibodies, Viral"[Mesh]) AND ("Infant, Premature"[Mesh])). Related articles in PubMed were also reviewed, as well as references described in these publications.

Inclusion criteria: preterm/very low birth weight

The publications were analyzed for:

1. Method used for analysing the samples.
2. Possible confounding factors, such as GA, BW, type of delivery and maternal age.

With the search, 18 relevant publications were found.

Characteristics of included studies:

Of the 18 selected studies, 10 studies specifically describe infants with a GA of less than 32 weeks.[26,28,84-90] Eleven studies used (in house or commercial) Enzyme-Linked Immuno Sorbent Assay (ELISA) [26,85,87-89,91-96], 2 studies used Hemaglutination Inhibition (HI) and neutralization tests (NT) [27,86], 1 study used a solid phase fluorescent immunoassay, called FIAX [84], 1 study used an enzyme-linked fluorescent immunoassay (VIDAS) [90], 1 study used immunofluorescent antibody to membrane antigen assay (IFAMA) [28], 1 study used micro-neutralization [97], and 1 study used a multiplex immunoassay (MIA)[98].

Direct comparison among the studies with different methods was not possible, except for the studies using International Standards. However within a study, we could compare preterm and term infants and their mothers.

Results

Measles (n= 8)

Measles antibody titers or percentages of protective measles antibody titers were lower in preterm compared with term infants or compared to their mothers (Table 3.1).[26,27,84,85,88,89,95,96] Preterm infants of vaccinated mothers had lower measles antibody concentrations than preterm infants of naturally infected mothers, since mothers who have suffered from measles have higher antibody concentrations.[27] In all studies that analyzed the transplacental transport ratio, the transplacental transport ratios in preterm infants were lower than in term infants. However, the amount of transplacental transport in preterm infants differed between the 3 studies (Table 3.2).[27,88,96] In the study of Linder et al.[27] very preterm infants <

Table 3.1. GMC/GMTs and percentages (%) of infants and mothers with a protective antibody level at birth.

			Preterm <32 weeks		Mothers		Preterm <37 weeks		Mothers		Term		Mothers	
	Assay	**Units**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**
Measles														
Leineweber[26]	ELISA	IU/ml	1270					96		96	4383	95		96
Özbek[88]	ELISA	OD	2.05	100	2.51	100	2.16	100	2.50	100	2.39	100	2.38	100
Rau [89]	ELISA	OD	1.11				1.22	92			2.35	100		
Gunes[85]	ELISA	IU/ml		76	295			88	302			100	288	
Wesumperuma [96]	ELISA	IU/ml					2.18	83		100	5.68	91		
Okoko [95]	ELISA	IU/ml					1.12‡				3.42			
Glick [84]	FIAX	FSU	23.5	55	42.2	86								
Linder [27]	HI	titer					7.0	50	7.5		14.6	81	11.7	
Rubella														
Doroudchi [91]	ELISA	IU/ml					70.8				87.5			
Leineweber[26]	ELISA	IU/ml	47*					90	78	86	123	98	78	86
Linder [86]	HI	titer	64.6	96	82.5		78.8	100	82.5		87.3	97	100.6	95
Glick [84]	FIAX	FSU	17.2	52	31.8	83								
Varicella														
Linder [28]	IFAMA	titer	2.5*	25*	10.4	100	10.5	95	12.6	95	12.6	95	10.4	93
Leineweber[26]	ELISA	mIU/ml	307*	96*	798	98					1060	98	798	98
Wesumperuma [96]	ELISA	AU/ml					0.96	89			2.50	91		
Okoko [95]	ELISA	AU/ml					2.13				5.34			

Table 3.1. GMC/GMTs and percentages (%) of infants and mothers with a protective antibody level at birth. (continued)

			Preterm <32 weeks		Mothers		Preterm <37 weeks		Mothers		Term		Mothers	
	Assay	**Units**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**
Hib														
Okoko [94]	ELISA	µg/ml					1.1				2.3			
Van den Berg [98]	MIA	µg/ml	0.15	46	0.67	84					0.28	70	0.37	76
Nagao [93]	ELISA						0.73		0.79		0.82		0.82	
Wesumperuma [96]	ELISA	µg/ml						83			-	95		
Difteria														
Van den Berg [98]	MIA	IU/ml	0.06	97	0.11	99					0.09	95	0.08	95
Okoko [95]	ELISA	IU/ml					1.10				2.76			
Wesumperuma [96]	ELISA	IU/ml					1.24	11			2.81	100		
Tetanus														
Van den Berg [98]	MIA	IU/ml	0.70		0.82						1.23		0.61	
Okoko [95]	ELISA	IU/ml					1.23				3.42			
Wesumperuma [96]	ELISA	IU/ml					3.62	100			4.67	100		
Mumps														
Leineweber [26]	ELISA	PEI/ml	5.3	63	6.5	62					10.3	73	6.5	62
Glick [84]	FIAX	FSU	18.7	45	79.2	97					-		-	
Ptx														
Heininger [92]	ELISA	EU/ml					13		11		17		11	

Table 3.1. GMC/GMTs and percentages (%) of infants and mothers with a protective antibody level at birth. (continued)

			Preterm <32 weeks		Mothers		Preterm <37 weeks		Mothers		Term		Mothers	
	Assay	**Units**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**	**GMC/T**	**%**
Van den Berg [98]	MIA	EU/ml	5.4		7.3						6.2		5.2	
Nomura [87]	ELISA	EU/ml	3.4#		3.8#		5.4		7.2		7.4		5.0	
FHA														
Heininger [92]	ELISA	EU/ml					14		17		33		17	
Van den Berg [98]	MIA	EU/ml	9.8		15.1						14.1		10.2	
Nomura [87]	ELISA	EU/ml	14.2#		13.7#		17.1		15.9		11.3		7.5	

ELISA: Enzyme-Linked Immuno Sorbent Assay, FIAX: solid phase fluorescent immunoassay, HI: Hemagglutination Inhibition MIA: Multiplex Immuno Assay, VIDAS: enzyme-linked fluorescent immunoassay

[a] <2500g

[b] <28 weeks

[c] <30 weeks

Table 3.2. Transplacental transport ratios

	Preterm < 32 weeks	Preterm < 37 weeks	Term
Measles			
Linder[27]	0.89		1.44
Wesumperuma[96]		1.51	2.03
Okoko[95]	0.62		1.01
Varicella			
Linder[28]	0.4[a]	0.92	1.14
Wesumperuma[96]	0.96		1.52
Okoko[95]	0.75		1.36
Hib			
Van den Berg[98]	0.26		0.74
Wesumperuma[96]		0.58	0.98
Okoko[94]		0.4	1.14
Diphtheria			
Van den Berg[98]	0.53		1.18
Wesumperuma[96]		1.03	2.39
Okoko[95]		0.72	1.43
Tetanus			
Van den Berg[98]	0.86		1.89
Wesumperuma[96]		1.13	1.33
Okoko[95]		0.86	1.79

Transplacental transport ratios are defined as the ratio between infant to maternal serum samples.
[a] GA<28 weeks

30 weeks had lower titers in the neutralization test than preterm infants >30 weeks. Similar results were found in the study of Gunes et al.[85] in which infants < 32 weeks had lower measles antibody titers than infants > 33 weeks. In the study of Leineweber et al.[26] the infant-maternal ratio reached 1 at 32 to 36 weeks. In follow-up studies[26,88,89], the majority of preterm infants had no protective measles antibody titers at 6 months of age.

Rubella (n=4)

Rubella antibody titers were lower in preterm infants than in term infants in all 4 included studies (Table 3.1).[26,84,86,91] In the studies of Leineweber et al. and Linder et al. more than 90% of the preterm infants had a protective rubella antibody titer.[26,86] However in the study of Glick et al.[84] only half of the preterm infants had protective rubella antibody titers at birth and all infants had significant lower antibody titers than their mothers. In the study of Linder et al.[86] very preterm infants <30 weeks had a lower percentage of protective antibodies compared with older (pre)term infants. In follow-up studies, none of the preterm infants

with a GA < 32 weeks, had positive Rubella antibody titers at 6 months of age[26] and in the study of Glick et al.[84] at 3 months of age.

Varicella-zoster (n=5)

Protective antibody rates were around 90% for all infants[26,28,90,95,96], except for the 25% of protective antibody titers in preterm infants with GA <28 weeks in the study of Linder et al.[28] Despite the high protective antibody rates, all studies found lower geometric mean titers (GMT) in preterm infants than in term infants. The infant-maternal ratio reached 1 at 32–36 weeks of gestation.[82,84] Very preterm infants <28 weeks in the study of Linder et al.[28] had lower antibody titers than both preterm >28 weeks and term infants. No positive anti-varicella-zoster antibody titers were found at 2 (1-3) months of age in preterm infants with a GA <28 weeks and at 6 months of age in preterm infants with a GA of 29-35 weeks.[28,84]

Mumps (n=2)

Mumps antibody titers were lower in preterm infants compared with term infants and maternal antibody levels.[26,84] Less infants had protective antibody titers in the study of Glick et al.[84] compared with the study of Wesumperuma et al.[96], although more mothers had protective antibody titers in the study of Glick et al. This can be explained by the lower GA of the infants in the study of Glick et al.[84] In the study of Glick et al.[84], also no positive antibody levels were found in preterm infants at 3 months of age.

Hib (n=4)

Infant-maternal ratios were lower in preterm infants compared with term infants (Table 3.1).[93,94,96,98] The infant-maternal ratios were higher in both preterm and term infants in the study of Wesumperuma et al.[96] than in term infants in the study of Okoko et al.[94] Okoko et al.[94] found higher GMTs for Hib in both preterm and term infants compared with the study of Nagao et al.[93]

Diphtheria (n=3)

GMTs and transport ratios were lower for preterm infants, compared with term infants.[95,96,98]

Tetanus (n=3)

IgG antibody levels in both preterm and term infants have been found above the protective cut-off for tetanus, in the studies of Wesumperuma et al.[96] and Van den Berg et al.[98] In the studies of Okoko et al.[95] and Van den Berg et al.[98], lower GMTs and lower transport ratios for preterm infants but higher GMTs and higher transport ratios for term infants have been found compared with the study of Wesumperuma.[96] Lower anti-tetanus antibody titers were found in preterm than in term infants in all studies.

Bordetella pertussis (n=3)

The vaccine components pertussis toxin (Ptx) and filamentous hemagglutinin (FHA) were measured in the study of Heininger et al.[92] and Nomura et al.[87] and Ptx, FHA, pertactin (Prn) and fimbriae (Fim) were measured in the study of Van den Berg et al.[98] Preterm infants with a GA <37 weeks had lower GMTs than term infants. In the study of Heininger, preterm infants had higher GMTs for Ptx than their mothers.[92] The infant-maternal transfer ratio reached 1 by 32 (FHA) and 33 (Ptx) weeks of gestation in the study of Heininger et al.[92]

Polio (n=1)

Infants had less protection than their mothers in this study of Linder et al.[97] Preterm infants had lower GMTs than term infants and lower maternal antibody transfer.

Influencing factors

A strong correlation between maternal and infant IgG concentrations for both preterm and term infants was observed in 8 of the included studies[26–28,86–88,90,91,93,97,98], while 3 of the included studies found this correlation only between term infants and their mothers.[28,87,93]

In 6 of the included studies, none of the measured antibodies was associated with parity[85,91,95,96,98] and maternal age[85,95,96] and maternal weight[94–96] or maternal height[85,96]. Leineweber et al found an increase of GMT against measles in mothers with increasing age.[26]

Wesumperuma et al.[96] found higher antibody titers for tetanus, diphtheria and varicella-zoster in non-anemic mothers and their infants compared with anemic mothers and their infants. Doroudchi[91] found lower maternal antibody titers for Rubella antibodies in mothers with one abortion or blood type B+. Low BW (<2.5 kg) was associated with lower antibody transfer for diphtheria[95,96] and varicella-zoster[95]. Maternal vaccination status influences IgG transport of measles antibodies in the study of Linder et al.[27] and Gunes et al.[85]. Vaccinated mothers have lower maternal antibody titers for measles than naturally infected mothers and, therefore, infants of vaccinated mothers had lower antibody titers than infants of natural immunized mothers.[27,99]

Discussion

Our review shows that the transplacental transfer of maternal antibodies against measles, rubella, varicella-zoster, mumps, Hib, diphtheria, tetanus, bordetella pertussis and polio is lower in preterm infants than in term infants. This difference is more pronounced in very preterm infants (GA <32 weeks) than in preterm infants with a GA of 32-36 weeks. There is a strong correlation between maternal and infant antibody concentrations and maternal vaccination status influences infant IgG antibody concentration.

Preterm infants with a GA <32 weeks had lower antibody levels compared with preterm infants with a GA >32 weeks, term infants and mothers. Leineweber et al.[26] showed that the infant-maternal ratio reaches 1 at 32 to 36 weeks for mumps, measles, rubella and varicella-zoster. In follow-up studies, with very preterm infants <32 weeks of gestation, the duration of protection against several vaccine- preventable diseases was shorter compared with term infants.[26,28,84,85,88,89] The majority of preterm infants <32 weeks had no protective antibody titers after 2-6 months for varicella-zoster and after 6 months for measles. These findings suggest that preterm infants are earlier and therefore longer at risk for varicella-zoster infection. Especially, as in large parts of the world varicella-zoster immunizations are no part of the immunization schedules and in other parts of the world these immunizations are only given after 12 months or more.[100] Measles vaccinations are also given after 12 months or at even later age. The few studies[26,28,84,85,88,89] in which infants are followed for 6 months after birth showed low levels of protection and rapid decrease of positive levels in the infants. Most of these studies included a low number (n=21-32) of infants, except for Rau et al.[89] (n=100). Therefore more follow up studies in preterm infants are needed.

In the literature we found that several factors influenced transplacental transport to term infants including maternal ethnicity, maternal vaccination status and maternal health (HIV/malaria). The included studies in this review were performed in different continents with mothers of different nationalities. The study of Hartter et al.[101] found higher transplacental transport of IgG in Nigerian mothers than in Germany. Mothers in Nigeria had higher total IgG and lower transplacental transport of both total IgG and anti-measle IgG compared with German mothers, indicating that the limited active placental transfer of measles IgG is associated with the higher maternal total IgG values found in Nigerian mothers.

Differences in vaccination status could also count for differences in protection against measles in preterm infants, because measles antibody titers in vaccinated woman are lower compared with naturally infected mothers.[27,85] HIV and malaria are known to diminish the transplacental transport.[102–104]

Some of the reviewed studies were performed in malaria or HIV epidemic areas[103–105] and could therefore show lower transplacental transport in infected mothers compared with healthy mothers. This could decrease the transplacental transport to preterm infants further and therefore increase the risk on infections with vaccine-preventable diseases.

The half-lives of maternal Varicella Zoster Virus IgG in preterm and term infants are 25.5 days[90] and 42-45 days[106] respectively. Therefore, preterm infants are even earlier at risk for vaccine-preventable diseases than term infants.

Possibilities to protect preterm infants against vaccine-preventable diseases during the period before they receive their first vaccination are maternal vaccination and/or administration of intravenous immunoglobulin. Maternal immunization during pregnancy could increase the maternal IgG concentrations and subsequently the level of transported antibodies to the infants. Studies with maternal immunization have been generally conducted

after 30 weeks of gestation[107-111] because little maternal antibody is transferred to the fetus until 28-32 weeks of gestation. Furthermore administration of vaccines after the fetus is more fully developed is more acceptable to mothers and investigators. A study of maternal Hib immunization showed that relatively small amounts of Hib-specific IgG antibody are transplacentally transferred to the fetus within a two-week period after immunization of the mother.[109] For preterm infants with GA <32 weeks, maternal immunization during pregnancy will not improve their protection against vaccine preventable diseases as they will not have received the maternal IgG antibodies at birth.[112] A recent review showed that administration of intravenous immunoglobulin for preventing infections in preterm and/or low BW infants gives a small reduction (3-4%) in nosocomial infections without a reduction in mortality or other important clinical outcomes.[113] Another possibility to protect preterm infants with lower antibody concentration after birth is an adapted immunization schedule, with earlier or extra immunizations compared to the schedule used in term infants.

Direct comparison of values of antibody concentrations retrieved from the included studies in this review was hampered due to different methods of measurement. ELISA is a more sensitive method than hemagglutination inhibition assay. Therefore, use of ELISA tends to result in more positive values as compared to hemagglutination inhibition,[114] which makes it difficult to compare studies with these different methods. However, comparison between preterm and term infants within a study is not influenced by the method of measurement.

In conclusion, the transplacental transport of maternal IgG against measles, rubella, varicella-zoster, mumps, *Haemophilus influenza* type B, diphtheria, pertussis and tetanus is lower in preterm infants than in term infants. IgG levels of preterm infants decrease earlier in life below the protective cut-off level than term infants, which puts preterm infants at risk for vaccine-preventable diseases even at an earlier age. Studies on adapted immunization schedules for pregnant women or for preterm infants are warranted.