ARTICLE

Exposure to non-inherited maternal antigens by breastfeeding affects antibody responsiveness

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ABSTRACT

The observation, by Ray Owen and colleagues in 1954, that D-negative women were less likely to form anti-D antibodies against their D-positive fetus if their mother possessed the D-antigen, was not found in all later studies. We hypothesized that breastfeeding, received by the mother, may affect her immunity against non-inherited maternal red blood cell antigens. We studied a cohort of 125 grandmother-mother-child combinations, from a follow-up study of mothers after intrauterine transfusion of the fetus for alloimmune hemolytic disease. For mismatched red blood cell antigens the mother was exposed to, whether or not antibodies were formed, we determined whether her mother, the grandmother, carried these antigens. The duration for which the mothers were breastfed was estimated by way of a questionnaire. Using multivariate logistic regression analyses, the interaction term (non-inherited maternal antigen exposure by categorized breastfeeding period) showed that a longer breastfeeding period was associated with decreased alloimmunization against non-inherited maternal antigens (adjusted odds ratio 0.66; 95% confidence interval 0.48-0.93). Sensitivity analysis with dichotomized (shorter versus longer) breastfeeding periods showed that this lower risk was reached after two months (aOR 0.22; 95% CI 0.07-0.71) and longer duration of breastfeeding did not seem to provide additional protection. These data suggest that oral neonatal exposure to non-inherited maternal red blood cell antigens through breastfeeding for at least two months diminishes the risk of alloimmunization against these antigens when encountered later in life.

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Introduction

In utero, all humans are exposed to non-inherited maternal antigens (NIMAs), however only pregnant women encounter inherited paternal antigens (IPAs). NIMAs and IPAs can involve the same antigens (Figure 1). Maternal antibodies against IPAs expressed on red blood cells (RBC) such as Rh and K antigens, can cause severe hemolytic disease of the fetus and newborn (HDFN).

In 1954, Owen and colleagues found that D-negative mothers were less likely to form anti-D against a D-positive fetus if they had previously been exposed to the D blood group as a NIMA, a phenomenon referred to as the "grandmother effect".[1] These findings seemed in accordance with the concept of neonatal tolerance in mice, published a year earlier by Billingham and collegues.[2] However, subsequent investigations did not confirm the grandmother theory.[3-5] Some studies even reported that a D-negative child may develop anti-D against the D NIMA.[6,7] As a result, the grandmother concept was almost forgotten.

Decades later, in 1988, Claas and colleagues observed that hyper-immunized dialysis patients awaiting renal allograft, formed antibodies against non-inherited

paternal HLA antigens (NIPAs) significantly more often than against NIMAs.[8] However, a protective effect of HLA NIMAs exposure on later renal and stem cell transplant outcome was not confirmed in all further studies.[9-11]

Studies in mice models showed that a maximum immune tolerance to NIMA is obtained when *in utero* exposure to NIMA is followed by breastfeeding (BF).[12,13] One study in humans showed a superior graft survival of maternal and sibling renal transplants when the recipient was breastfed.[14] Other studies in humans also showed that the duration of BF was associated with autoimmune diseases later in life.[15,16]

Therefore, the controversial results on the role of exposure to NIMAs on later immunity when challenged by pregnancy, transfusion or transplantation, may - among other factors - be due to different BF habits. Breast milk contains soluble molecules such as HLA, immunoglobulins and extracellular vesicles, as well as viable cells, the latter already observed by Antoni van Leeuwenhoek in the 17th century.[17–19]

Despite ante- and postnatal anti-D immunoprophylaxis since 1998, Rhesus D antibodies are still the most frequent cause of severe HDFN. We previously showed that, yearly, about 15 pregnancies complicated by anti-D, four by anti-K and one by anti-c required intra-uterine transfusions (IUT).[20] RhD immunoprophylaxis however hampers investigation of the effect of D NIMA exposure *in utero* and by BF on the anti-D response towards a D-positive child.

Severe HDFN is nowadays successfully treated with IUT. Unfortunately, such IUTs expose the mother to RBC antigens of the fetus and IUT donors, often leading to the induction of additional RBC antibodies.[21]

In the present study we investigated the hypothesis, that BF may affect immunity against non-inherited maternal red blood cell antigens, when encountered later in life through pregnancy or by transfusion, in a cohort of mothers whose fetuses were treated with IUT because of HDFN.

Methods

Study design

A cohort study of 125 grandmother-mother-child combinations, participating in the LOTUS (LOng Term follow Up after intrauterine transfusionS) study. In short, all women with children who were treated with IUT for HDFN from 1987-2008 were eligible. Details of the population and the methods adopted have been published previously[22] (see *Online Supplementary Appendix* for details). All participating women were asked to invite their mothers to participate. Grandmothers were asked to complete a questionnaire on duration of breastfeeding (regardless of exclusivity). The study was approved by the ethics committee of the Leiden University Medical Center (P08.080).

Data collection and intra-uterine transfusion policy

All participants and IUT donors were typed for relevant RBC antigens (see *Online Supplementary Appendix* for details). The mothers were screened for RBC antibodies as previously described.[23] Maternal transfusion history including date, number and donor of each IUT and number of pregnancies were collected. Over the years the transfusion policy changed with increasing degree of extended RBC antigen matching between mother and IUT donor and also procedural technique (see *Online Supplementary Appendix* for details).[20,24]

The following was determined:

1. Identification of non-D RBC antigens (C, c, E, e, K, Fy^a, Fy^b, Jk^a, Jk^b, M, S and s) expressed by the child or IUT donor(s) but not by the mother i.e., mismatched antigens.
2. The presence or absence of maternal antibodies against each of these mismatched antigens.
3. For each mismatched antigen, whether the grandmother carried the antigen as a NIMA.

Statistical analyses

Univariate logistic regression was used to calculate odds ratio (OR) and 95% confidence intervals (CIs). The presence of antibodies was used as the dependent variable. BF duration was analysed categorized as 0, 1, 2, 3, 4-6 and >6 months and in a sensitivity analysis dichotomized (≤ or > 0, 1, 2, 3, 4 and 6 months). Adjusted odds ratio (aOR) was calculated in the final multivariate logistic regression model. The following variables were considered potential confounders for RBC antibodies: ABO compatibility between mother and child, maternal HLA-DRB1*15 genotype,[25] number of IUTs (categorized as 1, 2, 3, 4 and >4), number of pregnancies (categorized as ≤2, 3 and >3), year of IUT (categorized in 5-year-blocks; 1988-93, 1994-98, 1999-03 and 2004-08) and RBC antigen immunogenicity (high: C, c, E, e and K and low: Fy^a, Fy^b, Jk^a, Jk^b, M, S and s antigens).

The associations between the duration of BF and the induction of antibodies were adjusted for potential confounders (i.e., *P*-values <0.2 in univariate analyses). To test for effect modification, two interaction terms (NIMA by months of BF and NIMA by antigen immunogenicity) were added to the model. The variables NIMA, months of BF, and the interaction term (NIMA by months of BF) were forced into the model.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA). A 95% CI not overlapping the null value 1.00 for OR was regarded statistically significant.

Results

Study population

A total of 125 grandmother-mother-child pairs participated in the study. The mothers (median age at follow up, 40 years; range 24-52) gave birth to 399 children of which 143 were treated for HDFN with a total of 405 IUTs. The median birth order of the first IUT-treated child was three; there were three cases with an affected first child. The antibodies primarily responsible for HDFN were anti-D (n=93), anti-K (n=19), anti-c (n=11) and anti-C^w and -Kp^a, one each (see Table 1 for additional characteristics).

A total of 549 RBC antigens - other than D - were not expressed by the mothers. For 171 of these antigens, there was no exposure by child or donor, and due to incomplete child and/or donor RBC typing, exposure was not known for 48 antigens. Consequently, analyses were restricted to the remaining 330 antigen exposures (median 3; range 1-5 per mother), of which 123 were NIMA re-exposures and 207 not previously exposed to as NIMA. These resulted in 158 antibodies, 54 (44%) against NIMA of which six antibodies caused the HDFN, and 104 (50%) against antigens not exposed to as NIMA, of which 26 caused the HDFN (Figure 2).

Breastfeeding duration and antibody responses

The median period that the 125 mothers were breastfed for was two months (range 0-12); 45 mothers were not

breastfed, 80 mothers for a median period of three months (Table 1).

Univariate analyses revealed that antigen immunogenicity (OR 17.3; 95% CI 10.0-29.9), number of IUTs (OR 1.22; 95 % CI 1.04-1.43) and IUT-year (OR 0.85; 95% CI 0.68-1.06) were associated (all $P<0.2$) with antibody formation. ABO compatibility, maternal HLA-DRB1*15 genotype and number of pregnancies were regarded not associated (all $P>0.5$) (Table 2).

Multivariate analysis showed that, high compared to low antigen immunogenicity, increasing number of IUTs and antigen exposure as NIMA compared to exposure not as NIMA were associated with an increased risk of having antibodies (aOR for the latter 3.28; 95% CI 1.38-7.80). A longer BF period showed a trend towards a higher risk for antibodies (OR 1.17; 95% CI 0.97-1.43). The interaction term (NIMA by categorized months BF) revealed that a longer BF period was associated with a decreased risk of antibody formation against NIMA (aOR 0.66; 95% CI 0.48-0.93) compared to antigens not exposed to as NIMA (Table 3).

Sensitivity analyses with dichotomized periods of BF showed that BF for at least two months compared to a shorter period, and NIMA exposure were associated with an increased risk for antibodies (aOR 2.39; 95% CI 1.12-5.13 and aOR 3.34; 95% CI 1.55-7.24, respectively). Again, the interaction term showed a decreased risk for antibodies against NIMA after at least two months BF (aOR 0.12; 95% CI 0.03-0.42). These associations remained when comparing at least three months BF to a shorter period. Continuation of BF beyond three months did not seem to provide additional protection against the formation of NIMA antibodies (Table 3).

For all analyses, antigen immunogenicity and number of IUTs were associated with an increased risk for antibodies, while IUT-year and the interaction term NIMA by antigen immunogenicity were not associated with antibody risk.

Discussion

The role of exposure to RBC-NIMAs during fetal or neonatal life on later development of (non-D) RBC antibodies after re-exposure to the antigens during pregnancy as IPAs or by transfusions was investigated in 125 three-generation families with a (grand)child with HDFN treated with IUT. In contrast to women who were breastfed for less than two months, BF for at least two months was associated with a significantly lower incidence of alloantibodies to NIMAs compared to the same antigens not previously encountered as NIMA.

The relevance of BF in the induction of tolerance against NIMA has mainly been studied in the context of the major histocompatibility complex (MHC) antigens in mice models.[12,26,27] These studies clearly showed that a maximal immunoregulatory effect to NIMA is obtained after exposure both *in utero* and by BF.[12,13] However, the underlying mechanism(s) remain elusive, and several immunological consequences of fetal/maternal interactions have been proposed both in mice and humans. BF in mice induced $Foxp3^{+}CD25^{+}$ T regulator cells potentially capable of regulating anti-maternal MHC immune responses.[13,28] BF

Table 1. Characteristics of the 125 mothers.

Characteristics	N (%)*
Age at follow up, median (range), years	40 (24–52)
BF duration in months, median (range)	2 (0-12)
No breastfeeding	45 (36)
One month	17 (14)
Two months	15 (12)
Three months	17 (14)
Four to six months	18 (14)
More than six months	13 (10)
Birth order of first IUT treated child, median (range)	3 (1–7)
Number of IUTs, median (range)	3 (1–10)
Maternal-fetal major ABO compatibility – N/N tested (%)	101/112 (90)
HLA-DRB1*15 positive	38 (30)
Antibody causing HDFN:	
Anti-D	93 (74)
Anti-K	19 (15)
Anti-c	11 (9)
Anti-Kp^{a} and -C^{w}	2 (2)

BF: breastfeeding; IUT: intra-uterine transfusion; HDFN: hemolytic disease of the fetus and newborn. *: Data presented as number (%) of women unless stated otherwise.

Table 2. Variables associated with RBC antibody formation after mismatched antigen exposures, univariate analysis.

Variables	OR	95% CI	P
RBC antigen immunogenicity (low** [non Rh, K] *vs.* high [Rh, K])	17.3	10.0-29.9	<0.001
Number of IUTs (1, 2, 3, 4 and >4)	1.22	1.04-1.43	0.014
IUT year (5-year blocks)	0.85	0.68-1.06	0.148
ABO compatibility** *versus* incompatibility	1.26	0.62-2.57	0.531
HLA-DRB1*15 genotype absent** *versus* present	1.10	0.69-1.75	0.689
Number of pregnancies (≤2, 3 and >3)	0.98	0.75-1.27	0.877
Exposure not as a NIMA** *vs.* NIMA re-exposure	0.78	0.50-1.21	0.265
Breastfeeding months (0, 1, 2, 3, 4-6 and >6)	0.98	0.87-1.10	0.721
Antibodies after NIMA-mismatched exposures	1.08	0.93-1.25	0.320
Antibodies after NIMA-matched exposures	0.82	0.67-1.01	0.062

RBC: red blood cell; OR: odds ratio; CI: confidence interval; IUT: intra-uterine transfusion; NIMA: non-inherited maternal antigen; [non Rh, K]: Fya, Fyb, Jka, Jkb, M, S and s antigens; [Rh, K]: C, c, E, e and K antigens; **: reference.

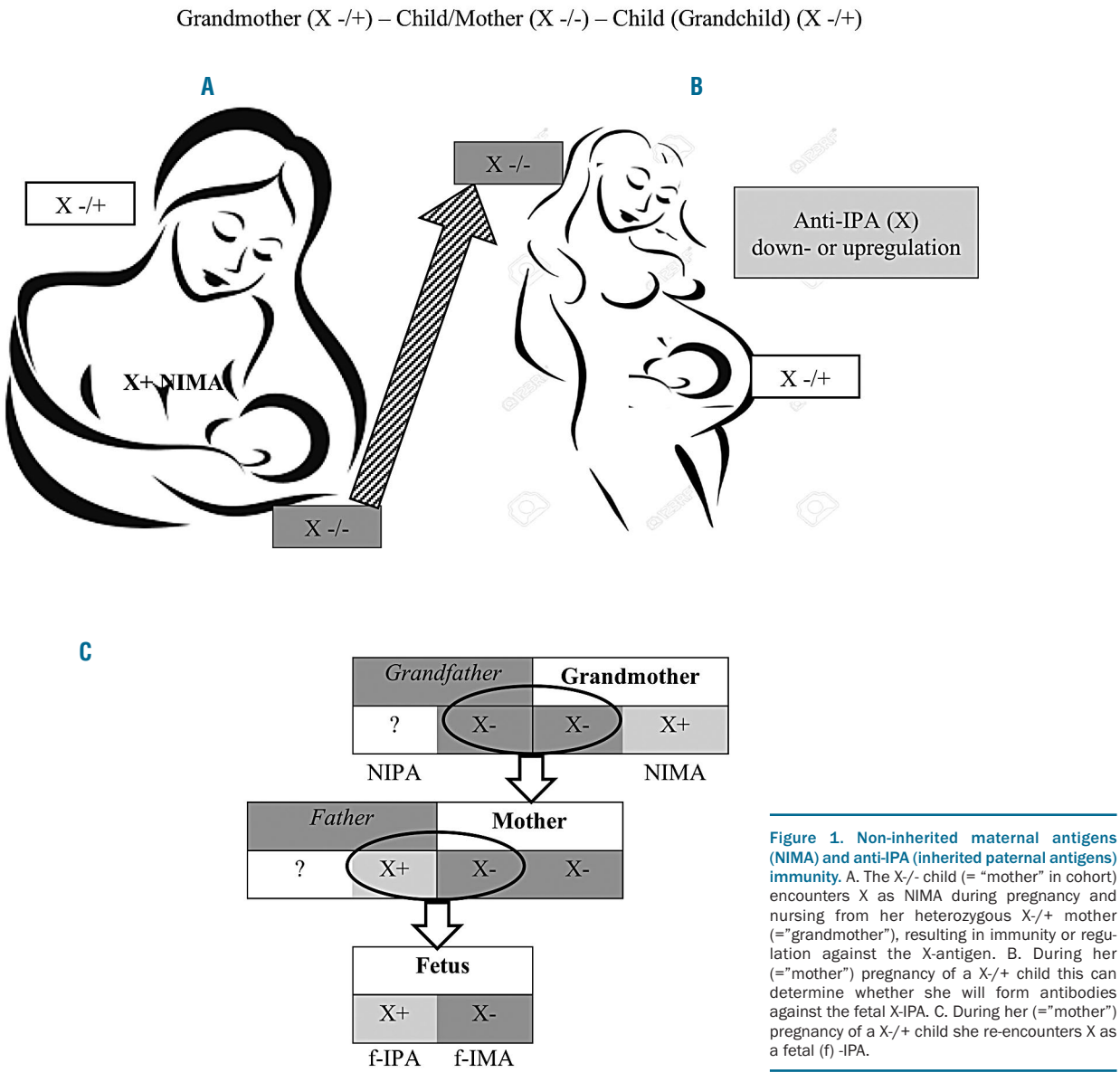

Figure 1. Non-inherited maternal antigens (NIMA) and anti-IPA (inherited paternal antigens) immunity. A. The X-/- child (= "mother" in cohort) encounters X as NIMA during pregnancy and nursing from her heterozygous X-/+ mother (="grandmother"), resulting in immunity or regulation against the X-antigen. B. During her (="mother") pregnancy of a X-/+ child this can determine whether she will form antibodies against the fetal X-IPA. C. During her (="mother") pregnancy of a X-/+ child she re-encounters X as a fetal (f) -IPA.

implies extended exposure to soluble and cellular maternal antigens and, in addition, extracellular vescicles (EVs) which can exert several immune effects. EVs are derived from a variety of cells including RBC, and several clinically relevant Rhesus, Kell, Duffy and Kidd blood group antigens are expressed.[29,30] Erythrocyte derived EVs have immunomodulating properties.[31] Up to 6 months after delivery, human colostrum and breast milk contains exosomes capable of increasing $Foxp3^{+}CD4^{+}CD25^{+}$ allospecific T regulator cells *in vitro*.[19] In the postnatal period, when the newborn is developing immunity against environmental threats, prolonged exposure to the maternal antigens may be perceived as auto-antigens requiring regulation. Moreover, oral exposure to antigens and antigen-antibody complexes was reported to induce regulation in neonates as well as in adults.[32,33] In D-sensitized women pregnant of a subsequent D-positive child, oral administration of D-antigen inhibited an expected boost in anti-D titer.[34] Finally, breast milk provides an additional source of viable maternal cells that may increase maternal microchimerism, which is considered a driving force of regulation leading to maintenance of tolerance for NIMAs.[18,35,36]

A different history of maternal BF may explain the discrepancy of finding a grandmother effect in various studies. Until manufactured baby milk became available, BF was part of our immunological education. Several, also cultural aspects, such as wealth and women's emancipation, often replaced BF by cow milk. This may however have consequences that are still unknown. Another aspect of BF is the transmission of maternal cells which seem to play a role in immunity against malignant diseases in the child as shown by Amatay and colleagues, based on a meta-analysis suggesting that BF may strengthen anti-leukemic immunity in progeny.[37]

Our observations on the effect of oral exposure to NIMAs by BF may not just explain the historical controversies regarding the grandmother theory. Why only a minority of individuals form RBC alloantibodies after pregnancy and/or blood transfusions (responders), while

Table 3. Variables associated with red blood cell antibody formation after mismatched antigen exposures, by categorized and dichotomized breastfeeding periods, multivariate analysis.*

BF duration	Breastfeeding		NIMA exposure**		NIMA by months BF	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Categorized						
0, 1, 2, 3, 4-6, >6	1.17	0.97-1.43	3.28	1.38-7.80	0.66	0.48-0.93
Dichotomized						
0 *vs.* >0	1.11	0.54-2.26	1.81	0.68-4.79	0.77	0.23-2.53
≤1 *vs.* >1	1.15	0.56-2.33	1.78	0.71-4.41	0.78	0.24-2.48
≤2 *vs.* >2	2.39	1.12-5.13	3.34	1.55-7.24	0.12	0.03-0.42
≤3 vs >3	1.95	0.83-4.59	2.49	1.23-5.06	0.41	0.03-0.59
≤4 *vs.* >4	1.34	0.53-3.43	1.77	0.92-3.39	0.37	0.07-1.98
≤6 *vs.* >6	1.08	0.35-3.32	1.55	0.83-2.92	0.86	0.13-5.61
<2 *vs.* >3	2.37	0.93-6.05	3.57	1.47-8.70	0.11	0.02-0.51
2 and 3 *vs.* >3	1.11	0.41-2.96	1.15	0.36-3.69	0.35	0.07-1.80

*The complete table 3, including results from the variables, Immunogenicity, Number of IUTs, Year of IUT and the interaction term NIMA by Immunogenicity are in the *Online Supplementary Appendix*. BF: breastfeeding; NIMA: non-inherited maternal antigen; aOR: adjusted odds ratio; CI: confidence interval; **The reference is incidence of antibodies after exposure not as a NIMA.

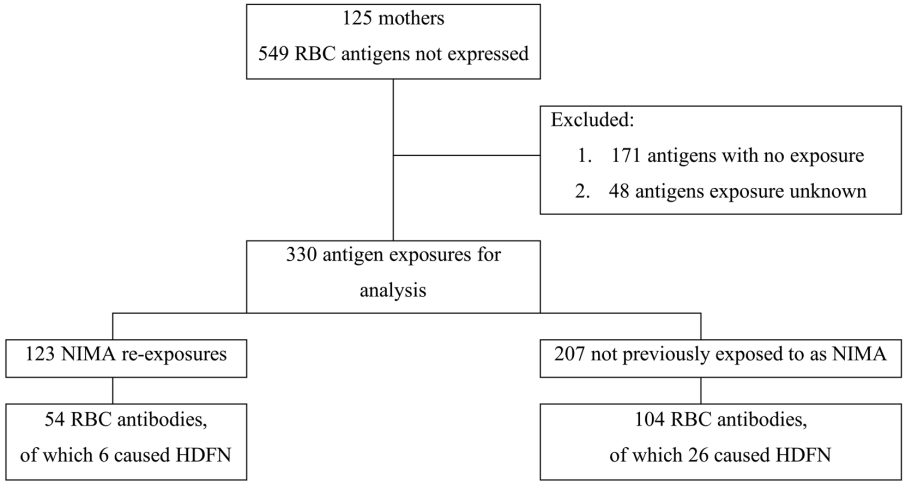

Figure 2. Study flowchart of 125 mothers exposed to 330 non-D RBC antigens and antibody response. RBC: red blood cell; NIMA: non-inherited maternal antigen; HDFN: hemolytic disease of the fetus and newborn.

others do not, despite multiple exposures to mismatched RBC antigens (nonresponders), has yet to be unravelled and considered to be multifactorial. Factors such as antigen immunogenicity and dose, route of exposure, race, age, co-existence of inflammation during RBC antigen exposure, genetic factors (such as HLA and immunoregulatory gene polymorphisms), and medical (immunosuppressive) conditions have all been reported to enhance or ameliorate RBC alloantibody formation.[38-42] The duration of exposure to NIMA by BF adds a new aspect to this already complex question.

Limitations

Firstly, our study cohort - similar to the HLA immunized cohort on the renal transplant waiting list, mentioned before[8] - consisted of highly immunized individuals, already possessing at inclusion at least one strong RBC antibody causing HDFN. We previously showed that once individuals produced an RBC antibody, there is over a 20% risk of forming additional antibodies upon subsequent exposures.[21,43] The results in these extensively allo-exposed young women, of which 80% formed antibodies against multiple RBC antigens after delivery, may not be generalizable for first RBC antigen encounter and for immune-compromised patients. Secondly, unidentified or unknown antigen exposures that had not resulted in RBC antibodies may have been missed; however, it is likely that these were equally distributed in the distinct BF periods. Thirdly, Owen and colleagues evaluated anti-D formation in relation to the D-NIMA. As a result of RhD immunoprophylaxis, we could not repeat Owen's design, however we did find support for a grandmother effect to non-D NIMAs after oral exposure by more than two months BF. Fourthly, the duration of BF was assessed through a questionnaire. BF was given decades before this study, and memory may not be exactly accurate. Lastly, in agreement with Owen, our study is hypothesis-generating and needs corroboration before drawing any definitive conclusion.

In conclusion, in women with HDFN-affected children, prolonged oral exposure to non-D NIMA by BF was associated with a significantly lower incidence of antibody production when later challenged to these NIMAs com-

pared to exposure to the same antigens not previously exposed to as NIMAs.

Ray Owen and colleagues concluded their 1954 publication on the grandmother theory with these words: "Presentation of this hypothesis here, on the basis of admittedly limited data, is justified by the hope that others in a position to test it will be encouraged to do so."[1]

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