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Maternal and Infant Secretory Immunoglobulin A across the Peripartum Period

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Abstract

Background: Salivary secretory immunoglobulin A (sIgA) concentrations change over early infancy. The primary immunoglobulin in breast milk is sIgA, however, no study has examined the role of maternal sIgA in relation to infant salivary sIgA.

Objectives: This study aimed to examine within-source associations and mean level changes of maternal and infant sIgA across the first 6 months of life, to examine the interrelations between maternal and infant sIgA across the first 6 months of life, and to determine the association between breastfeeding and infant sIgA.

Methods: Participants were a convenience sample of 51 mother–infant dyads. Salivary sIgA was collected from the mother in the third trimester. Infant and maternal salivary and maternal breast milk sIgA was collected at approximately 1, 3, and 6 months postpartum.

Results: Maternal salivary sIgA showed no mean level change across the visits, and levels were moderately associated over time. Breast milk sIgA was moderately associated over time; infant salivary sIgA was weakly associated over time. Both breast milk and infant sIgA levels decreased from 1 to 3 months postpartum. Maternal salivary sIgA was not related to infant or breast milk sIgA. Breastfed infants had lower levels of salivary sIgA. Likewise, higher concentrations of breast milk sIgA were related to lower concentrations of infant sIgA.

Conclusion: Maternal salivary sIgA is highly stable over the peripartum period, whereas breast milk and infant salivary sIgA was variable. Infant secretory IgA development does not depend positively on maternal salivary or breast milk sIgA.

Keywords

breastfeeding, breast milk, immunity, mothers and infants, salivary sIgA

Well Established

Secretory immunoglobulin A (sIgA) provides defense against oral pathogens and is the primary immunoglobulin found in breast milk. Newborn infants produce very little salivary sIgA, and breast milk sIgA is thought to provide "passive vaccine" to the developing infant.

Newly Expressed

Maternal salivary sIgA concentrations did not change over the peripartum, but breast milk and infant salivary sIgA concentrations decreased from 1 to 3 months postpartum. Breast milk sIgA and breastfeeding were related to lower infant sIgA.

Background

Secretory immunoglobulin A (sIgA) is the predominant mucosal immunoglobulin and plays a primary role in defending against invading pathogens. The common mucosal immune system includes the salivary glands, and antibodies produced in the salivary glands are thought to be indicative of mucosal immune competence[1] and children's mucosal immune development.[2] During pregnancy, increases in tissue inflammation and microorganisms in the oral cavity have the potential to affect oral mucosal immunity.[3] Perhaps in response, salivary sIgA levels have been found to be as much as 30% higher in pregnant women compared to nonpregnant controls.[4,5] Studies of intra-individual differences in salivary sIgA have found sIgA to increase from the second to the third trimester[6] and then decrease soon after parturition.[7]

At birth, infant serum and secretory IgA levels are undetectable; maternal serum IgA does not cross the placenta and infants do not start producing their own sIgA in tears, nasopharyngeal secretions, or saliva until the infant is roughly 1 to 2 weeks old.[8] Following this time of immune incompetence, longitudinal studies find a rapid increase in infant

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salivary sIgA, usually peaking between 4 and 6 weeks of age[9] and then declining to lower levels between 3 and 6 months.[9,10] Conversely, Fitzsimmons and colleagues[11] found a rapid increase across the first 4 months and then a plateau until their last measurement at 18 months. These discrepant findings highlight the intra-individual differences in the ontogeny of mucosal immunity across early childhood and suggest intermediary forces influencing the trajectory of sIgA expression during the early postpartum period.

The primary immunoglobulin found in human breast milk is sIgA,[12] and breast milk is thought to supplement infant mucosal sIgA levels.[13] Mammary glands are part of an integrated network of the mucosal immune system, and antibodies within breast milk reflect antigenic responses from the mother's gut and her respiratory system.[14] Therefore, the antibodies that infants receive are specific to pathogens in their environments. Although breastfeeding does not affect full-term infants' systemic immunity,[15] breastfeeding provides "passive vaccine" to the infants' upper airways and gut by offering infants additional protection against common infectious agents.[16-19] Breast milk sIgA also matures infant epithelial cells,[20,21] prevents infant reactivity to indigenous microbiota,[22] and reduces infant inflammation.[21]

No studies have longitudinally examined both maternal and infant sIgA to determine if infant sIgA development depends positively on maternal sIgA. Furthermore, we aim to examine longitudinal associations within each source of sIgA (ie, maternal and infant saliva, and breast milk) as well as changes in sIgA concentrations over time. We hypothesize that, first, within-source sIgA will be highly correlated across time but show mean level decreases across the first 6 months of life; second, maternal salivary sIgA will be positively related to breast milk sIgA, and both maternal salivary and breast milk sIgA will be positively related to infant salivary sIgA; and third, breastfeeding will be associated with higher concentrations of infant sIgA.

Methods

Procedure

The current study was approved by the institutional review board at Purdue University. Prior to participating in the study, mothers gave informed consent for themselves and their unborn child. Home visits (HVs) were scheduled during the third trimester of pregnancy (HV1), 1 month postpartum (HV2), approximately 1 month after the mother returned to work (HV3), and 6 months postpartum (HV4) on days when mothers were home with their infants (Table 1). Home visits were scheduled around 4:00 PM to control for any potential diurnal rhythm in sIgA. Saliva, breast milk (if breastfeeding), height/length, and weight were collected at all visits. Participants were compensated $15 at HV1, $20 at HV2 and HV3, and $25 at HV4.

To control for any influence of daycare participation on infant sIgA levels and to create a sample consistent with most US infants' experience, all mothers recruited indicated that they would be returning to work after the birth of their child. HV3 was scheduled to occur approximately 1 month after the infant was placed in nonmaternal care.

Measures

Breastfeeding. The Breastfeeding Status Questionnaire[23] was administered at each of the postpartum HVs. Infants who derived nutrition solely from breast milk were classified as exclusively breastfed. Infants who derived nutrition solely from formula were classified as exclusively formula fed. Breastfeeding status was determined by a dichotomous variable asking the mothers, "Are you currently breastfeeding?"

Secretory immunoglobulin A. Mothers expelled approximately 2 mL of saliva into a cryogenic vial. Breastfeeding mothers expressed a small amount of breast milk (~ 1 mL) either manually or by breast pump into a cryogenic vial. Infant saliva was collected by trained experimenters using a highly absorbent hydrocellulose swab designed specifically for saliva collection in infants (Salimetrics, State College, Pennsylvania, USA). The swab was placed in the infant's mouth until the lower third of the swab was saturated. The time required to complete the saliva collection was noted to calculate flow rate. Infant intake of breast milk, formula, or other dairy products was restricted for 20 minutes prior to the saliva collections.

Samples were transported on ice and remained frozen at −80°C until assay. All samples were assayed for sIgA using an indirect enzyme immunoassay (Salimetrics). The sIgA assay uses 25 µL of saliva and has a sensitivity of 2.5 µg/mL. Assays were run in duplicate and the average of the duplicates was used in all analyses.

Analytical strategy. The 3 main objectives of these analyses were to, first, determine the within-source associations of sIgA and changes in mean concentrations of sIgA across the first 6 months of life; second, determine the interrelations between maternal and infant sIgA across the first 6 months of life; and third, determine the association between breastfeeding and infant sIgA. Given the susceptibility of null hypothesis testing and the increased likelihood of type II error with a small sample, we relied on effect sizes (Cohen's *d*) in conjunction with significance testing.

Analyses examining within-source associations and changes in mean concentrations (first objective) employed multilevel models with either breast milk, maternal salivary, or infant salivary sIgA as the outcome. Multilevel models account for the inherent nesting of longitudinal data and incorporate standard error adjustments that account for these correlations.[24] For the within-source association models,

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Table 1. Demographic and Biometric Characteristics of the Mothers and Infants at Each of the 4 Home Visits.[a]

	Home Visit 1[b]	Home Visit 2	Home Visit 3	Home Visit 4
Dyads, No.	51	49	47	45
Infant female, %		47	47	49
Breastfed, %		85.7	72.3	64.4
Exclusively breastfed, %		60.8	52.9	31.4
Exclusively formula fed, %		13.7	23.5	29.4
Infant age, wk	35.85 (0.88) ± 0.12	4.38 (0.35) ± 0.05	15.27 (3.96) ± 0.57	26.62 (0.95) ± 0.14
Infant flow rate, mL/min		0.15 (0.11) ± 0.02	0.42 (0.21) ± 0.03	0.77 (0.44) ± 0.06
Maternal time since waking, h	8.00 (3.55) ± 0.55	5.24 (2.75) ± 0.4	8.00 (3.71) ± 0.54	8.37 (3.45) ± 0.5
Infant time since waking, h		0.80 (0.93) ± 0.13	1.57 (1.57) ± 0.23	1.35 (1.18) ± 0.18
Maternal BMI, mass/height^2	30.13 (5.15) ± 0.74	26.49 (4.73) ± 0.7	26.02 (4.95) ± 0.74	25.59 (4.79) ± 0.74
Infant weight, lb	7.49 (0.94) ± 0.14	9.58 (1.19) ± 0.17	13.83 (2.13) ± 0.31	16.95 (1.81) ± 0.27
Infant length, in	20.37 (0.88) ± 0.13	21.53 (0.71) ± 0.10	24.36 (1.22) ± 0.18	26.09 (1.14) ± 0.17
Maternal salivary sIgA, μg/mL	183.46 (101.8) ± 14.26	195.36 (100.78) ± 14.4	163.86 (77.34) ± 11.28	169.10 (75.94) ± 11.32
Breast milk sIgA, μg/mL		575.87 (299.62) ± 46.79	411.16 (174.15) ± 29.87	448.10 (164.19) ± 30.49
Infant salivary sIgA, μg/mL		170.87 (181.33) ± 27.34	51.24 (42.22) ± 6.16	41.40 (22.29) ± 3.32

Abbreviations: BMI, body mass index; sIgA, secretory immunoglobulin A.
[a]Means, and percentages where indicated, are reported. Standard deviations are in parentheses, with ± the standard error of the mean (SEM) below.
[b]For home visit 1, infant age represents weeks gestation, infant weight represents birth weight, and infant length represents birth length.

sIgA at each HV was predicted by the sIgA at the previous HV (eg, HV2 to HV3). A piecewise approach with dummy codes of the HVs was used to estimate longitudinal change in mean levels of sIgA. For the second objective, within the piecewise longitudinal models, interrelations between sources of sIgA levels across time were examined. For the third objective, measures of breastfeeding were added to the longitudinal model predicting infant sIgA.

Results

A convenience sample of pregnant women was recruited through infant CPR and breastfeeding classes offered by local hospitals and parenting networks in a small Midwestern town. From these classes, 106 women expressed initial interest; of that, 17 did not fit inclusion criteria and 38 withdrew before their first HV, resulting in 51 mothers completing the first HV. Inclusion criteria included non-high-risk pregnancies, no chronic health illnesses, and plans of returning to work within 3 months of delivery. Mothers' ages ranged from 19 to 41 years (M [SD] = 29.1 [4.39] years). The majority were married (90.2%), primiparous (92%), and Caucasian (90.2%). The modal household income fell between $30 000 and $49 000 (range, less than $10 000 to more than $110 000). Forty-seven percent (n = 23) of the infants in the study were female. Mothers had on average 9.6 weeks of maternity leave. At HV4, 60% of the infants were cared for outside of the child's home, 39.5% were cared for in their home by a relative or babysitter, and 1 child was cared for in their home by their mother in the mother's in-home daycare.

Missing Data and Transformations

Of the 51 pregnant mothers who completed HV1, 49 completed HV2, 47 completed HV3, and 45 completed HV4. Out of the 438 potential samples (192 maternal saliva, 141 infant saliva, and 105 breast milk samples), 5 infant saliva samples were missing (insufficient sample for assay) and 1 breast milk sample was missing (maternal refusal). Full information maximum likelihood estimation (FIML) was carried out in SAS 9.2 on all multilevel models. To correct for skewed distributions, sIgA levels were log transformed and Winsorized by setting all outliers to 3 standard deviations beyond the mean. Two maternal and 2 infant values were Winsorized.[25] All skewness statistics were below 1.0 after the transformations.

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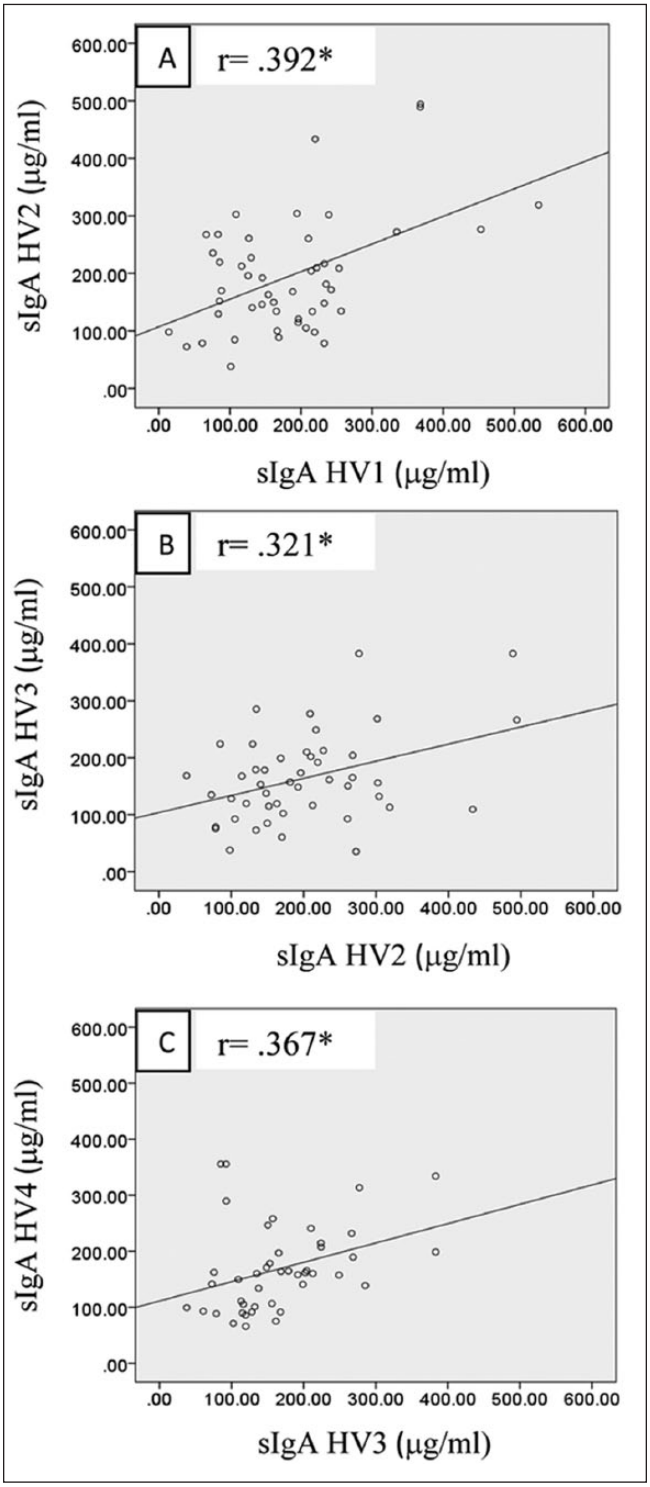
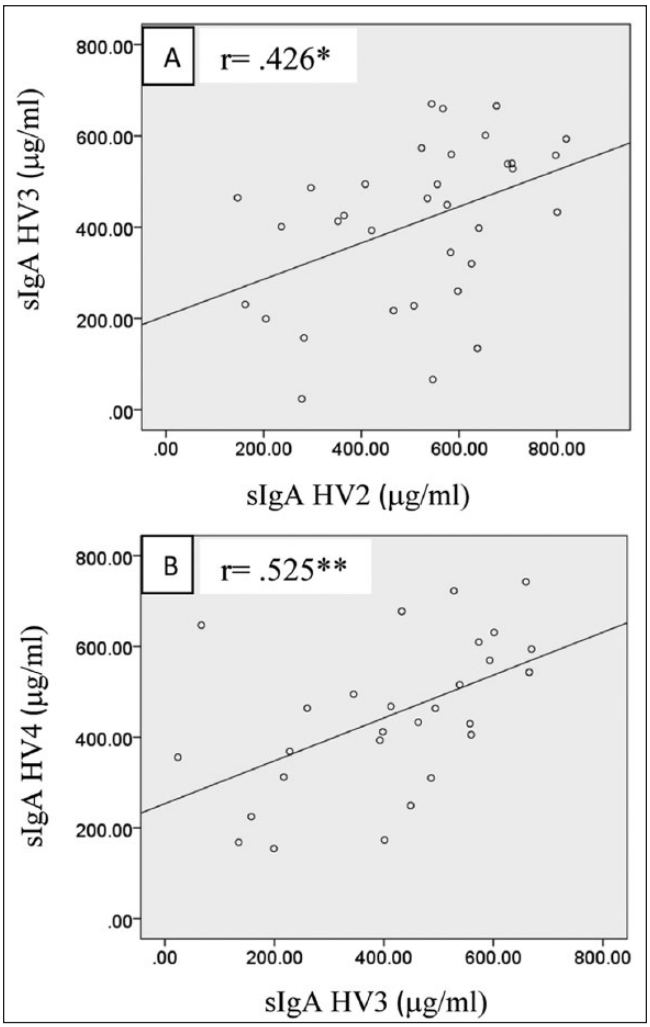
Figure 1. Maternal Salivary sIgA: Associations across Home Visits.



(A) Association between maternal salivary sIgA at HV1 and HV2, (B) association between maternal salivary sIgA at HV2 and HV3, and (C) association between maternal salivary sIgA at HV3 and HV4.
Abbreviations: HV1, home visit 1; HV2, home visit 2; HV3, home visit 3; HV4, home visit 4; sIgA, secretory immunoglobulin A.
*$P < .05$.

Figure 2. Maternal Breast Milk sIgA: Associations across Home Visits.



(A) Association between breast milk sIgA at HV2 and HV3, and (B) association between breast milk sIgA at HV3 and HV4.
Abbreviations: HV2, home visit 2; HV3, home visit 3; HV4, home visit 4; sIgA, secretory immunoglobulin A.
*$P < .05$.
**$P < .01$.

Associations within sIgA Source and Changes in Mean Levels of sIgA within Mothers and Infants

Early maternal sIgA production was longitudinally associated with her later sIgA production for both saliva (b = .347, $P < .0001$; Figure 1) and breast milk sIgA (b = .409, $P < .0001$; Figure 2). Infant salivary associations increased in strength across the visits (b = .531, $P < .0001$; Figure 3), with stronger correlations from HV3 to HV4 than HV2 to HV3. Maternal salivary sIgA concentrations did not change across the HVs (Ps > .200). Breast milk sIgA exhibited a 28.6% decrease from HV2 (M [SD] = 575.87 [299.62] μg/ml) to HV3 (M [SD] = 411.16 [174.15] μg/ml; b = .491, $P < .001$) but did not change from HV3 to HV4. Infants' sIgA concentrations

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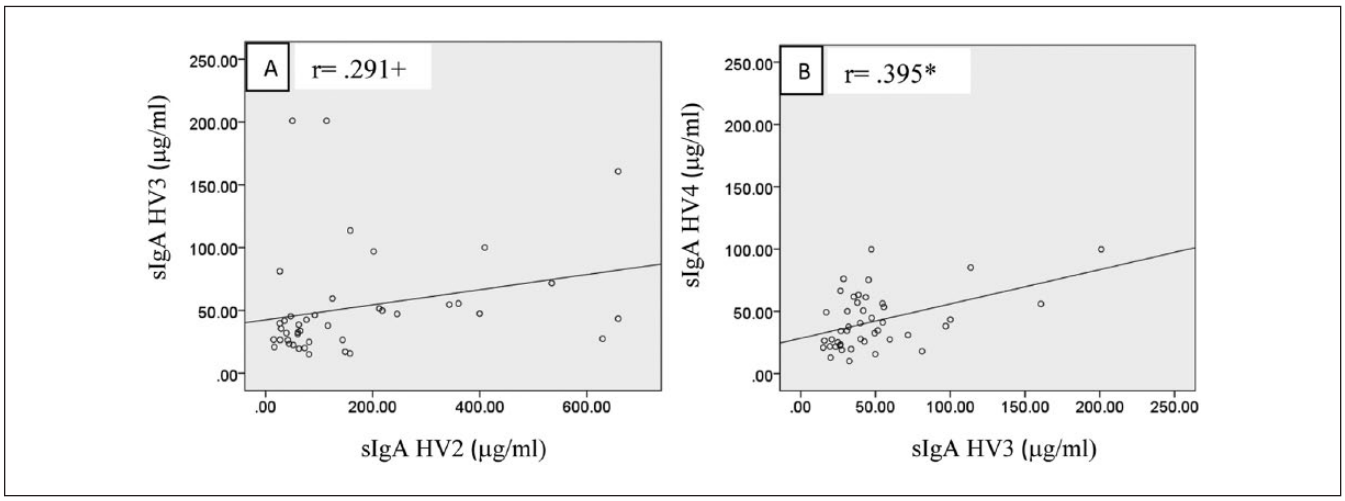
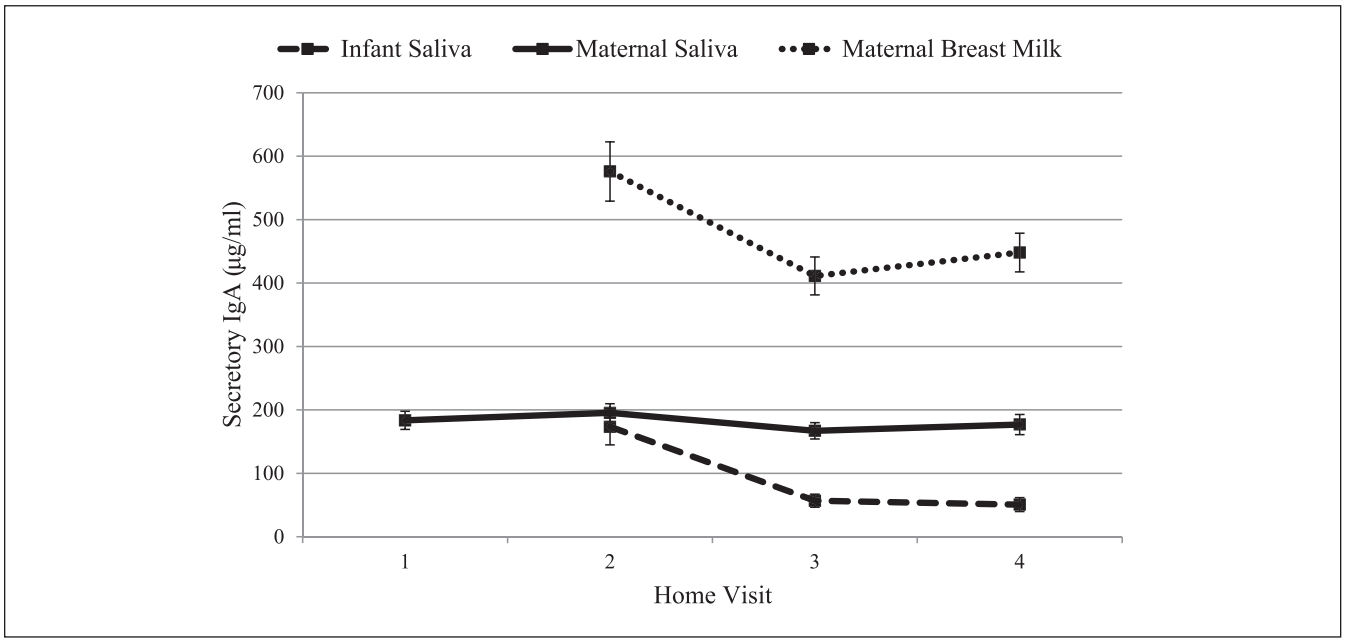
Figure 3. Infant Salivary sIgA: Associations across Home Visits.



(A) Association between infant salivary sIgA at HV2 and HV3, and (B) association between infant salivary sIgA at HV3 and HV4.
Abbreviations: HV2, home visit 2; HV3, home visit 3; HV4, home visit 4; sIgA, secretory immunoglobulin A.
+ $P < .10$.
*$P < .05$.

Figure 4. Salivary and Breast Milk Secretory Immunoglobulin A (IgA) Levels (µg/ml) from the Third Trimester of Pregnancy to 6 Months Postpartum.



Error bars indicate standard error of the mean (SEM).

decreased by 67.2% from HV2 (M [SD] = 170.87 [181.33] µg/mL) to HV3 (M [SD] = 51.24 [42.22] µg/ml; b = .909, $P < .001$) but did not change from HV3 to HV4 (Figure 4).

Interrelations of sIgA across Sources of sIgA

Comparing maternal salivary to breast milk sIgA revealed breast milk sIgA concentrations to be roughly 150.9% to 194.8% (380.51-247.3 µg/ml) higher than salivary sIgA concentrations (b = .950, $P < .0001$; Figure 4). Furthermore, maternal salivary sIgA concentrations were not associated with breast milk sIgA concentrations (b = .094, $P = .352$; Table 2). Maternal salivary (b = 1.03, $P < .0001$) and breast milk sIgA levels (b = 2.00, $P < .0001$) were significantly higher than infant sIgA levels. The difference between breast milk sIgA and infant sIgA was most pronounced at HV4, with breast milk sIgA (M [SD] = 448.10 [164.19] µg/ml) almost 10 times higher than infant salivary sIgA (M [SD] = 41.40 [22.29] µg/ml; Figure 4). Maternal salivary sIgA concentrations were consistently unrelated to infant sIgA

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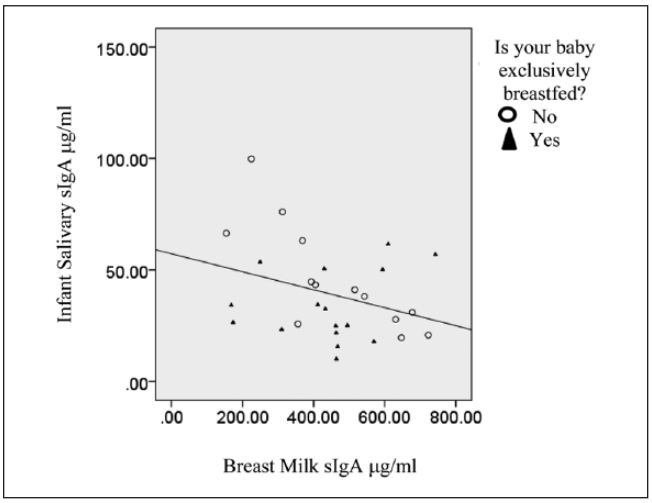
Table 2. Correlations of Maternal Salivary (Maternal), Breast Milk, and Infant Salivary (Infant) Secretory Immunoglobulin A at Each of the 4 Home Visits (HV1-HV4).

Variable	1	2	3	4	5	6	7	8	9	10
1. Maternal HV1	—									
2. Maternal HV2	.392*	—								
3. Maternal HV3	.282+	.321*	—							
4. Maternal HV4	.415*	.266+	.367*	—						
5. Breast milk HV2	–.088	.121	.181	.061	—					
6. Breast milk HV3	.211	.091	–.028	.352*	.426*	—				
7. Breast milk HV4	.025	.132	.022	.438*	.603**	.525**	—			
8. Infant HV2	–.072	.044	–.223	–.023	.030	.174	.075	—		
9. Infant HV3	.135	.311*	–.216	.044	.120	.028	.251	.291+	—	
10. Infant HV4	.111	.003	–.104	.104	.065	–.030	–.322+	.056	.395*	—

+*P* < .10.
**P* < .05.
***P* < .01.

Figure 5. Association between Maternal Breast Milk Secretory Immunoglobulin A (sIgA) and Infant Salivary sIgA at Home Visit 4, by Exclusive Breastfeeding Status.



concentrations (b = –.033, *P* = .684; Table 2). No association between breast milk sIgA and infant sIgA was found at HV2 or HV3; however, at HV4, mothers with greater amounts of sIgA in their breast milk had infants with lower levels of salivary sIgA (b = .366, *P* = .05; Figure 5).

Association between Breastfeeding and sIgA

There was no difference in sIgA concentrations between breastfed and nonbreastfed infants (b = –.03, *ns*). Because most mothers at HV2 (85.7%) and HV3 (72.3%) were breastfeeding, analyses were re-run examining breastfeeding at HV4 only. Although not statistically significant (b = –.25, *ns*), Cohen's *d* suggests that breastfeeding has moderate practical significance (*d* = .27) for infant salivary sIgA levels at 6 months (breastfed: M [SD] = 39.2 [20.56] µg/ml; formula fed: M [SD] = 45.40 [25.33] µg/ml). Similarly, across all the visits, there was no statistically significant difference in salivary sIgA in infants who were exclusively breastfed (n = 16) compared to exclusively formula fed (n = 15). Again, analyses were examined at HV4 only (b = –.39, *ns*). Cohen's *d* suggests that exclusive breastfeeding at 6 months has large practical significance (*d* = .48) for infant salivary sIgA concentrations at HV4. On average, exclusively breastfed infants (M [SD] = 33.7 [16.04] µg/ml) had sIgA concentrations that were 21% lower than exclusively formula-fed infants (M [SD] = 42.7 [23.8] µg/ml).

Discussion

Counter to previous examinations,[7] concentrations of maternal salivary sIgA did not change across the 4 home visits and produced relatively small standard deviations. Likewise, mothers' salivary sIgA exhibited moderate within-person associations, meaning that mothers' early production of sIgA was moderately associated with later production. For infants, these early months following birth are an immunologically complex time of maturation and sensitization of the new immune system,[10] and our findings of increasing strength of visit-to-visit associations might reflect this maturational process. Specifically, whereas infants' sIgA concentrations at 1 month were very weakly associated with 3-month concentrations, concentrations at 3 months were more strongly related to 6-month concentrations. In fact, infants' 3- to 6-month associations were similar to those seen in maternal salivary sIgA. Similar to past studies, we found that infants had adult-like levels of salivary sIgA at 1 month, but they dropped approximately 70% by the 3- and 6-month assessments.

At 6 months, breastfed infants had lower sIgA than nonbreastfed infants, and this difference was even more pronounced when comparing exclusively breastfed to exclusively formula-fed infants. Although these associations did not reach conventional significance, findings from within the breastfed infants did. Specifically, mothers with higher levels of breast milk sIgA had infants with lower levels of salivary sIgA. Together, these analyses suggest that any exposure to maternal breast milk is associated with lower infant antibody activity, and this differential is linked to the amount of mammary antibodies produced.

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Reduced infant sIgA could be an artifact of measuring total sIgA, as opposed to antigen-specific sIgA. Perhaps, breastfed infants have lower levels of total sIgA because of more effective sIgA responses to specific antigens. Breast milk sIgA is thought to be important in the maturational process of infant epithelia cells, which are responsible for the secretion of sIgA,[21] and therefore it is possible that greater maturation of the breastfed infant's immune system allows for a more accurate response to environmental antigens. In support of this idea, breastfed infants have been shown to have lower resting lymphocyte concentrations but more robust immune responses to vaccines.[26] In other words, formula-fed infants might require greater production of antibodies to achieve the same resistance as breastfed infants. A follow-up study examining infant oral bacterial load in breastfed and formula-fed infants and infant salivary and breast milk sIgA to those specific antigens would be useful. Specifically, future studies could test the hypotheses that, first, infant antigens and breast milk antigen-specific antibody production are positively associated; second, breast milk antigen-specific antibody production and infant antigen-specific antibody production are negatively associated; and third, the link between antigen load and infant antigen-specific antibody responses is weaker in breastfed compared to formula-fed infants.

Conversely, formula could be affecting infant oral and systemic health. Formula-fed infants are at an increased risk of caries due to a wide range of formulas that lower oral pH and increase cariogenic bacteria. Breast milk does not have the same pH-reducing properties, nor does it appear to support bacterial growth.[27] It is possible that the heightened salivary sIgA in the formula-fed infants may be a reaction to localized oral infection of opportunistic bacteria due to oral changes fostered by formula. Thus, lower levels of sIgA in breastfed infants may reflect lower antigen burden. Tests for oral bacteria load in conjunction with assays specific to those bacteria will help elucidate the causes of the relationships presented in the current study.

Due to the small sample size and homogeneous nature of the participants, particularly with respect to socioeconomic status and race/ethnicity, this analysis was a preliminary investigation into the immunological profiles of mothers and their young children. Cultural differences play a large role in determining how and what infants eat, and thus this study may serve as a reference for future studies of other populations. Furthermore, the immune system is incredibly complex, made of numerous cell types (sometimes working in opposition[28]) that are compartmentalized (eg, blood vs bile vs saliva[29]), such that the dynamics of immune function will be different based on the location and the immune factor in question. Thus, the results presented do not generalize to circulating IgA, sIgA from other membranes, or other immune factors.

Conclusion

Maternal salivary sIgA is highly stable over the peripartum period, whereas breast milk and infant salivary sIgA were variable. Infant sIgA development does not depend positively on maternal salivary (or breast milk) sIgA. Future explorations should examine antibody responses to specific antigens to potentially elucidate the process by which maternal sIgA leads to a reduction in infant sIgA.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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