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Original Article

Factors associated with secretory IgA levels in colostrum and breastimilk

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Abstract

Background Secretory IgA (sIgA) content of breastmilk in the first postpartum month is a reflection of the pregnant woman's immune response to environmental antigen exposure. The role of secretory IgA in breastmilk is to protect and support the development of the neonatal immune response in early life.

Objective To examine possible factors associated with sIgA levels in breastmilk and colostrum, including environmental exposure, food consumed, maternal history of atopy, and the appearance of allergic symptoms in infants. As a secondary objective, we determined the association between infant factors (IgE, exposure to cigarette smoke) and maternal factors (sIgA, maternal allergies) with infant allergies.

Methods This prospective cohort study of 80 postpartum mothers and their infants was conducted at Sultan Agung Islamic Hospital, Semarang, Central Java. We collected maternal colostrum on the second or third postpartum day and mature milk between the 22nd to 25th postpartum day. Exposure factors to mothers and infants in the final trimester of pregnancy up to one month postpartum was recorded through a questionnaire and home visits. The infant's IgE level was measured at 4 months of age.

Results Mean colostrum sIgA was 108.9 (SD 16.5) mg/dL (95%CI 97.9 to 121.1 mg/dL) and mean mature milk sIgA was 94.1 (SD 23.9) mg/dL (95%CI 89.1 to 99.2 mg/dL). Mean colostrum sIgA levels were higher in mothers exposed to cigarette smoke [119.1 (SD 1.7) *vs*. 92.9 (SD 1.5) mg/dL; P=0.026] and frequent infections [128.2 (SD 1.7) *vs*. 95.9 (SD 1.6) mg/dL; P=0.007] compared to that in unexposed mothers. Mean colostrum sIgA was also higher in mothers with atopic allergy than in those without (136.8 mg/dL *vs*. 99.3 mg/dL; P=0.017) and in mothers of infants with IgE levels >29 IU/mL than in mothers of infants with IgE levels <29 IU/mL (136.8 *vs*. 101.2 mg/mg/dL; P=0.045). Elevated colostrum sIgA (>136.8 mg/dL) was not associated with allergies in the infants (P=0.269).

Conclusions Maternal atopic allergy and frequent infections are associated with increased colostrum sIgA levels. Breastmilk sIgA levels are not associated with allergies in the infant. Maternal exposure to antigens may stimulate the production of specific breastmilk sIgA. **[Paediatr Indones. 2023;63:13-21; DOI: 10.14238/pi63.1.2022.13-21**].

Keywords: *maternal allergy; colostrum sIgA; total IgE; infant allergy*

The incidence of allergic and autoimmune diseases have increased worldwide. According to the hygiene hypothesis theory, this phenomenon is related to a decrease in infectious diseases, leading to an imbalance in the immune response of T-helper 1 (Th1) and T-helper 2 (Th2) cell subsets.[1] Normal early-life immune responses are expected to prevent allergic diseases, as well as autoimmunity in adulthood. The neonatal immune response is influenced by immune cells and antibodies from maternal milk.[2]

The prevalence rate of allergic asthma in Indonesia is lower than that in other Southeast Asian countries. In 2003, the prevalence is 3.6%, lower than that in Thailand, Malaysia, and the Philippines.[3] The *Riset Kesehatan Dasar/Riskesdas* (*Indonesian Basic Health Survey*) 2018 reported asthma rates of 1% to 4.5% in different provinces. Infection was still the most common class of diseases.[4] The lower number of allergic diseases in Indonesia, therefore, still needs to be investigated with regards to background and environmental factors.

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Breastmilk is a very important part in the early development of newborn immunity. It contains secretory IgA (sIgA) and regulatory cytokines. Other bioactives in breastmilk maintain a balance between sensitization and tolerance to external antigens. Secretory IgA (sIgA), a component of breastmilk, can strengthen the immune barrier in the intestines and increase intestinal regulatory cytokines (TGF-β, IL-10) that support the presence of T-regulators. T-regulators maintain Th2/Th1 balance, preventing polarization of the Th2 subset and thereby preventing allergy.[2,5,6]

Secretory IgA binds to antigens originating from food, commensal microbes, pathogens, and viruses. sIgA entraps pathogens in mucus for elimination, otherwise maintains the presence of commensal microbes, as well as modulates tolerance of the mucosal immune system to food antigens. The role of sIgA maintains a tolerant immune response to food allergens and commensal microbes, suppresses proinflammatory cytokines thereby preventing hypersensitivity reactions of the immune system.[5,6]

Previous studies on the role of breastmilk sIgA preventing infant allergies have had differing results. Savilahti et al. reported that casein-specific sIgA levels were associated with allergies in 4-year-olds, but found no evidence of an association between total sIgA and the incidence of allergies.[7]

Since research on breastmilk sIgA in Indonesia is limited, we wanted to examine possible associations between environmental factors, behavior, and history of maternal atopy with breastmilk sIgA levels during the last three months of pregnancy through the first month postpartum. In addition, we aimed to assess the association between breastmilk sIgA and the appearance of allergic symptoms in infants.

Methods

This study was part of a prospective cohort study on the incidence of infant allergy. Observations of mothers and their healthy babies were carried out for at least six months after delivery. The study was conducted in the Obstetric Polyclinic and Maternal/Delivery Ward, Sultan Agung Islamic Hospital, and the Child and Maternal Health Polyclinic of Bangetayu Primary Health Care in Semarang, Central Java, Indonesia. Subjects were recruited by consecutive sampling of all maternity patients from September to November 2017. Inclusion criteria were healthy pregnant women of ≥37 weeks' gestation without known fetal complications.

Maternal and infant health history data were obtained through home visit interviews using a questionnaire administered 3 times a month for 4 months or until the baby was 4-month-old. Furthermore, health monitoring was carried out by contacting mothers by mobile phone until their babies were 9-month-old.

The maternal medical history data obtained during the last trimester of pregnancy until one month postpartum included history of frequent infections, exposure to cigarette smoke from household members, the presence of pets (cats, dogs, or birds) inside the house, and history of recurrent allergy symptoms and their triggering allergens. History of infection was defined as the appearance of symptoms such as fever with or without common cold, cough, runny nose, or diarrhea, with a frequency of two times or more within the past 3 months.

History of maternal atopic allergy symptoms was assessed using a modified questionnaire based on the *White Book on Allergy*,[8] and diagnoses were confirmed by internists and/or dermatologists. Past history of skin allergies according to Hanifin and Rajka's criteria included urticaria symptoms with or without eczema with at least monthly attacks, and/or diagnosis of skin allergy by a dermatologist.[9] History of allergic atopy was confirmed with a positive skin prick test.

Symptoms of infant allergy were based on the *International Study of Asthma and Allergies in Childhood* (ISAAC) and Hanifin-Rajka criteria.[9,10] Diagnoses of infant atopy were based on the presence of allergy symptoms accompanied by a positive skin prick test (SPT) done after the baby was six months old.

Colostrum was obtained on the second or third postpartum day, whereas mature breastmilk was obtained between 22-25 days postpartum. We measured total sIgA levels using the ELISA sandwich technique kit *MBS703555* (*MyBiosource*, San Diego, California) at the GAKI laboratory, Universitas Diponegoro, Semarang. Eighty infants underwent total IgE measurements using chemiluminescent immunometric assay (*Siemens*, Washington DC), a quantitative technique, at *Prodia Laboratory*,

Semarang.

Skin prick tests were performed on mothers who had participated in the study for at least 4 months and on infants who showed allergic symptoms, including atopic dermatitis, recurrent chronic cough, and recurrent wheezing. Allergens tested included house dust, mites, crab, shrimp, chicken egg yolk, chicken egg white, cow's milk, cat dander, bird feathers, and grass pollen. Subjects were required to avoid antihistamines or corticosteroids for at least 1 week prior to undergoing SPTs.

This study was approved by the Ethics Committee for Medical and Health Research, Universitas Diponegoro Medical School. Analyses using *SPSS v. 21 software* (*IBM*, Armonk, New York) included comparative hypothesis testing of sIgA levels between two groups using independent sample t-test, and data normality testing using Kolmogorov-Smirnov. Data are presented in the forms of narrative, tables, and figures.

Results

There were 88 mothers who agreed to participate and continued in the study for up to two months after birth, 80 of whom agreed to SPTs. Seventeen mothers were confirmed to have atopic allergies based on positive SPT results and had evidence of allergy symptoms. Fourteen infants had symptoms of allergy (atopic dermatitis, recurrent wheezing, or chronic recurrent cough), but only nine had positive SPTs, hence, these nine infants were suspected of having atopic allergy. The study flowchart is shown in **Figure 1**.

The mean colostrum sIgA level from 80 mothers was 108.9 (SD 16.5) mg/dL (95%CI 97.9 to 121.1), with a median of 103.5 mg/dL. Mean mature breastmilk sIgA concentration was 94.1 (SD23.9) mg/dL (95%CI 89.1 to 99.2). **Table 1** shows the mean sIgA levels of colostrum and mature breastmilk according to subjects' characteristics through the first two months postpartum. There were no significant differences in mean sIgA levels in either colostrum or mature breastmilk between groups according to subject characteristics such as maternal age, gestational age, parity, nutritional status, place of residence, and mode of delivery.

Table 2 illustrates the analysis of maternal environmental factors (exposure to pets and cigarette smoke, history of infection, and consumption of various foods during pregnancy) and total colostrum /mature milk sIgA levels. Colostrum sIgA levels in the group of mothers with a history of infection were higher than in those without (P=0.007). In addition, colostrum sIgA levels in the group of mothers exposed to cigarette smoke were higher compared to the unexposed group (P=0.026). There were no significant associations between sIgA levels and history of frequent consumption of eggs, cow's milk, and shellfish, in either colostrum or mature breastmilk

Figure 2a shows that colostrum sIgA levels were significantly higher in mothers with atopic allergy than in those without [mean difference after logarithmic transformation 1.4 (95%CI 1.1 to 1.8; P=0.017)]. Significantly higher maternal sIgA level (136.8 mg/dL) was noted in infants with high IgE levels (>29 IU/mL) compared to infants with IgE <29 IU/ML (**Figure 2b**).

As shown in **Table 3**, of the 13 infants with high IgE, none were considered to have allergies. One of the infants with high IgE had symptoms resembling allergy but negative SPT and was therefore not considered to have atopic allergy. Neither maternal history of allergy, high infant IgE levels, high colostrum sIgA, nor maternal exposure to cigarette smoke were significantly associated with infant allergy (**Table 3**).

Discussion

In our study, most infants with high IgE levels at the age of 4 months showed no allergy symptoms. Unexpectedly, the group of infants with high IgE levels had a higher mean maternal colostrum sIgA level. These findings suggest the possibility that colostrum sIgA can prevent allergy symptoms in infants. However, this requires further study as it was not the primary outcome of our study. The immune system of pregnant women tends to be Th2-dominant in order to increase immunotolerance against foreign antigens, to protect the embryo from elimination by the mother's own immune system.11 The dendritic cells and macrophages of pregnant women release more cytokines, including IL-10 and TGF-β, which are immunotolerant. So, it can be understood that breastmilk is rich in sIgA, considering the formation

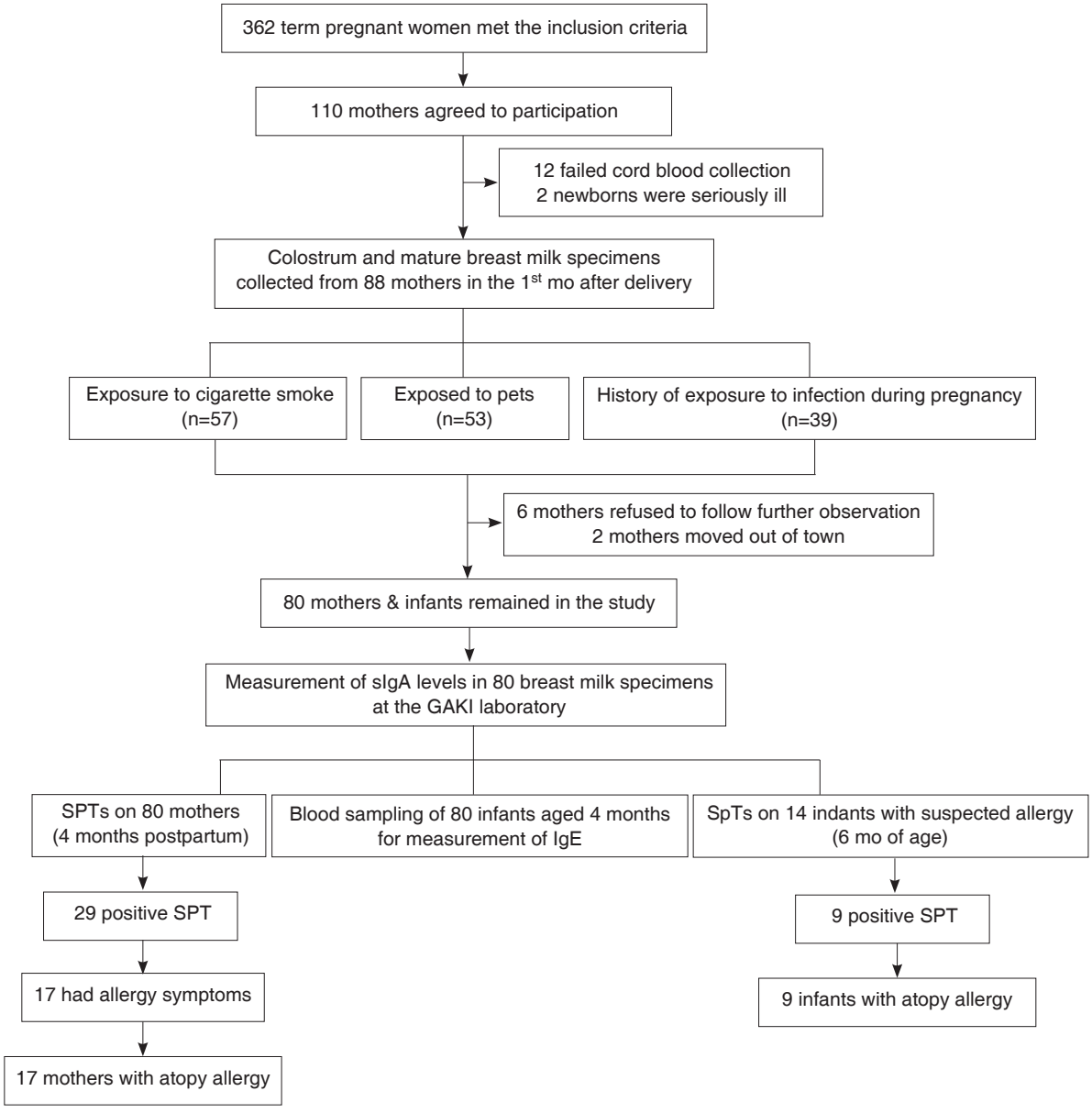

Figure 1. Study flow chart

of isotype switching of antibodies by B cells under the influence of regulatory cytokines IL-10 and TGF-β.[12] We noted that high colostrum sIgA levels in atopic mothers could lead to protection against allergic symptoms in their infants during the first 6 months, based on evidence that only 3/17 babies born to atopic mothers had allergies (**Table 3**). However, we found no evidence that high total colostrum sIgA levels was protective against allergy in infants.

According to the hygiene hypothesis, individuals who live in clean environments are more prone to allergies or autoimmunity.[1] In animal studies, mice given low doses of lipopolysaccharide had more regulatory T-cells (Tregs) in their gut than those raised in germ-free conditions. Exposure to components of Gram-negative bacteria also prevented allergic inflammation to house dust mites in the lungs.[13] In accordance with this study, our maternal subjects

Table 1. Analysis of colostrum and mature breast milk IgA levels by subjects' characteristics (N=88)

Variables	n (%)	Colostrum sIgA level			Mature milk sIgA level		
		Mean (SD), mg/dL	Mean comparison (95%CI)	P value*	Mean (SD), mg/dL	Mean difference (95%CI)	P value
Age							
17-35 years	75 (85.2)	108.4 (1.7)	0.9	0.787	92.9 (23.4)	-8.5	0.241
>35 years	13 (14.8)	113.0 (1.5)	(0.7 to 0.8)			(-22.8 to 5.8)	
Gestational age							
37-39 weeks	63 (71.6)	108.4 (1,6)	0.98	0.873	93.1(24.1)	-3.6	0.531
>39 weeks	25 (28.4)	110.7 (1,7)	(0.8 to 1.3)			(-14.9 to 7.7)	
Malnourished during pregnancy							
Yes	15 (17.0)	93.5 (1.5)	0.8	0.197	88.5(21.8)	-6.8	0.316
No	73 (83.0)	112.5 (1.7)	(0.006 to 1.1)			(-20.4 to 6.7)	
Residence							
Demak	53 (60.2)	104.0 (1.7)	0.9	0.466	91.1 (24.3)	-5.1	0.328
Semarang	35 (39.8)	112.5 (1.6)	(0.7 to1.2)			(-15.5 to 5.2)	
Mode of Delivery							
Vaginal	15 (17.0)	107.4 (1.5)	0.9	0.898	93.9 (20.8)	-0.2	0.962
Caesarian section	73 (83.0)	109.4 (1.7)	(0.8 to 1.3)			(-13.9 to 13.3)	
Number of gestations							
Primigravida	30 (34.1)	115.6 (1.8)	1.1	0.475	90.3 (20.0)	-5.3	0.331
Multigravida	58 (65.9)	106.4 (1.6)	(0.9 to 1.4)			(-15.9 to -5.4)	

*Unpaired T-test

Table 2. Analysis of colostrum/mature breast milk IgA levels and medical history and environmental exposures (N=88)

Maternal factors	n (%)	Colostrum sIgA level			Mature milk sIgA level		
		Mean (SD), mg/dL	Mean comparison (95%CI)	P value*	Mean(SD), mg/dL	Mean difference (95%CI)	P value*
Exposure to pets							
Yes	53 (60.2)	108.1 (2.2)	1.1 (0.8 to 1.2)	0.859	97.0(23)	7.3 (-3.1 to 17.6)	0.165
No	35 (39.8)	110.4 (1.6)			89.8(25)		
Exposure to cigarette smoke							
Yes	57 (64.8)	119.1(1.7)	1.3 (1.0 to 1.6)	0.026	93.1 (23.8)	-3 (113.7 to 7.7)	0.577
No	31 (35.2)	92.9 (1.5)			96.1 (24.6)		
History of infection							
Yes	39 (44.3)	128.2 (1.7)	1.3 (1.1 to 1.7)	0.007	94.4 (22.5)	0.5 (-9.8 to 10.8)	0.925
No	49 (55.7)	95.9 (1.6)			93.9 (25.3)		
History of frequent consumption of eggs during pregnancy	60 (68.2)	101.9 (1.6)	0.1 (0.7 to 1.0)	0.064	94.3 (23.8)	0.6 (-10.4 to 11.6)	0.914
Yes	28 (31.8)	126.5 (1.8)			93.7 (24.9)		
No							
History of frequent consumption of cow's milk during pregnancy							
Yes	57 (64.8)	107.8 (1.7)	0.9 (0.8 to 1.2)	0.783	93.1 (25.3)	-2.9 (-13.6 to 7.7)	0.579
No	31 (35.2)	111.2 (1.6)			96.1 (21.4)		
History of frequent consumption of shellfish during pregnancy							
Yes	12 (13.6)	93.3 (0.6)	0.8 (0.6 to 1.1)	0.254	92.2 (20.5)	-2.6 (-17.1 to 12.6)	0.764
No	76 (86.4)	111.4 (1.7)			94.4 (24.6)		

*Unpaired T-test

with history of infection had higher colostrum sIgA levels. According to a previous study, infants who lived in Estonia, a region with higher infections rates, had higher salivary sIgA levels compared to infants in Sweden.[14] Similarly, breastmilk from mothers who were previously infected with SARS-CoV-2 during pregnancy contained significantly higher sIgA levels compared to that of control mothers who delivered

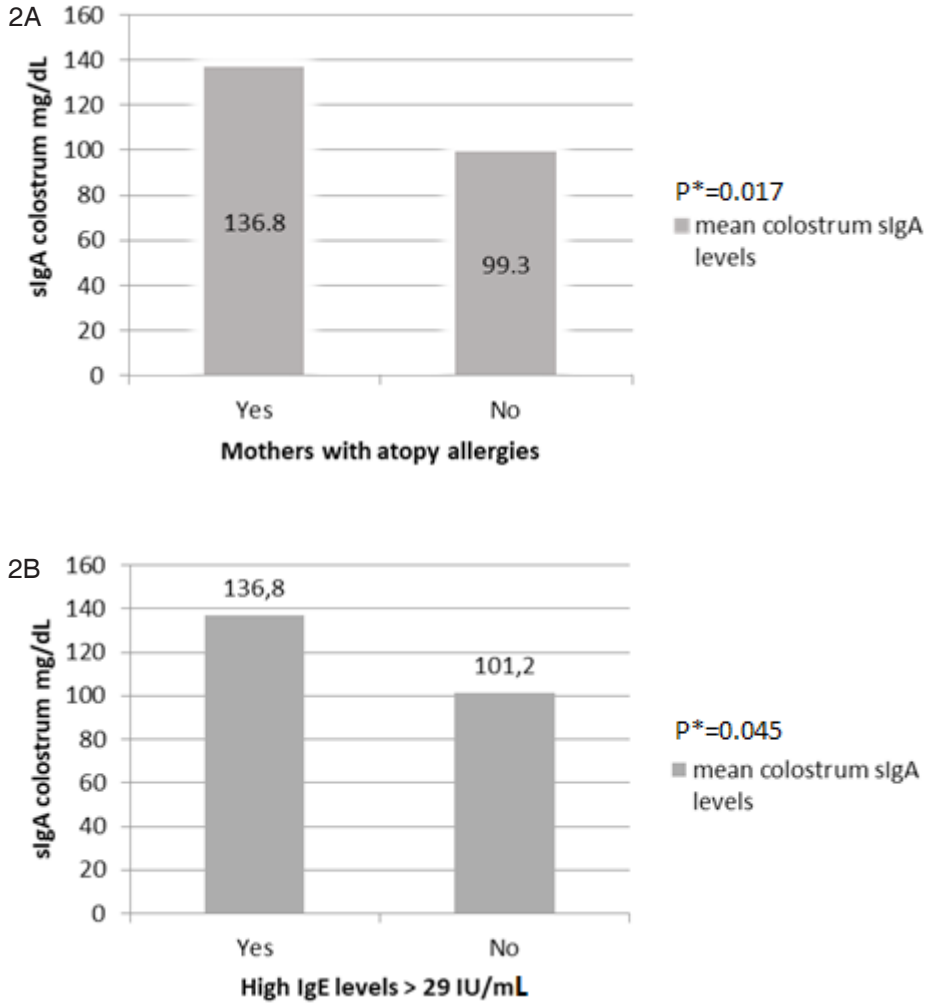

Figure 2. Colostrum sIgA levels by presence of (a) maternal atopic allergy and (b) high IgE levels

Table 3. Analysis of maternal and infant characteristics with infant allergy

Maternal/infant factors	Infants with allergies	Infants without allergies	P value*
Allergic mothers, n (%)			
Yes	3 (3.8)	14 (17.5)	0.374
No	6 (7.5)	57 (71.5)	
High infant IgE**, n (%)			
Yes	0 (0)	13 (16.3)	0.161
No	9 (11.3)	58 (72.5)	
High colostrum sIgA***, n (%)			
Yes	4 (5)	19 (23.8)	0.269
No	5 (6.3)	52 (65)	
Maternal exposure to cigarette smoke, n (%)			
Yes	8 (10)	8 (10)	0.111
No	1 (1.3)	1 (1.3)	

*Chi square test, **>29IU/mL, ***>136.8mg/dL)

before the COVID-19 pandemic.[15]

In our study, the median sIgA level in colostrum was 103.5 mg/dL, higher than that found in a Melbourne study (70 mg/dL).[16] This could be related to the higher prevalence of acute respiratory infections and diarrhea in Indonesia.4 High exposure to microbes can stimulate Th1 cells and dendritic cells to release the regulatory cytokines IL-10 and TGF-β, which would in turn stimulate the class transfer of B-cell antibody synthesis towards sIgA in the mucosa of pregnant women. This may explain the higher levels of colostrum and breastmilk sIgA in our study compared to that in previous studies.

Higher colostrum sIgA levels may initiate the newborn intestinal immune response that limits proinflammatory cytokines, strengthens epithelial barriers, and tends to be immunotolerant to antigens, including potential allergens. The mechanism of transport of the commensal microbial sIgA-microbial complex across the intestinal epithelium plays an important role in the development of the infant immune response. In line with the hygiene hypothesis, living in an environment with more frequent contact with infections actually reduces the incidence of allergies.[1,5,6]

Intestinal commensal organisms play a role in sIgA formation, as commensal bacteria stimulate IgA class switching because of the large number of intestinal dendritic cells that release TGF cytokines.[5,6] In Indonesia, there is a high level of consumption of tofu and tempeh, which has been shown to increase levels of IgA and A. muciniphila in human feces.[17] Therefore, further research is needed on the commensal microbiota of pregnant women in Indonesia in relation to their dietary consumption habits.

During pregnancy, the increase in commensal flora inhibits other pathogens, while preventing excessive inflammation.[18] Immune tolerance of commensal bacteria is presumed to increase Treg colonization; adequate amounts of Treg facilitate tolerance to antigens, including food-derived antigens, referred to as food Ag-specific Tregs. Tregs have heterogeneous properties that function differently in homeostasis, as well as certain commensal bacteria that can stimulate bacteria-derived Treg.[19]

An Iranian study reported that low salivary IgA was found in smokers who had dental caries,[20] but another study noted no significant correlation between salivary IgA and smoking quantity index.[21] In contrast, our maternal subjects exposed to cigarette smoke had higher colostrum sIgA levels compared to the unexposed group. Exposure to cigarette smoke may decrease resistance of the mucosal epithelium, making it more susceptible to bacterial or viral infections.[22] This condition may be followed by dendritic cells, B cells, and T cells responding to dangerous infectious/pollutant antigens by forming more IgA class-switching B cells. This homeostatic mechanism is likely to protect babies from pollutants.[18,19,22]

A previous in vitro study demonstrated that exposure to cigarette smoke stimulates proinflammatory cytokines by increasing IL-8 and neutrophil chemoattractants, but, conversely, decreases the cytokines TNF-α, IL-6, IFN-α, and IFN-γ-induced protein. Cigarette smoke causes increased inflammatory reaction, but reduces the immune defense against infections such as viruses.[22] The role of sIgA saliva in preventing dental caries has been well studied, but has not been shown to directly protect teeth.[20]

We found no association between maternal dietary habits, including the frequent consumption of shellfish during pregnancy, and breastmilk sIgA levels. Atopic mothers had high colostrum sIgA, but almost all of these mothers were allergic to house dust mites, while a few were allergic to foods such as crab, egg yolk, and cow's milk. In contrast, Lee et al. noted that the most common cause of allergies in Asia was shellfish.[23] Study is needed to determine the advantages or disadvantages of respiratory exposure to house dust mites for pregnant women, especially on colostrum sIgA levels.

A study in Aceh stated that most symptoms of allergic dermatitis and wheezing were found in the first 6 months of age.[24] Similarly, a previous study reported that atopic dermatitis was the most common allergic symptom in the first two months of life, followed by recurrent wheezing or chronic cough with wheezing from two to six months of age. They also noted that very early formula feeding before one month of age and lower umbilical cord zinc levels were associated with the incidence of allergy in infants.[25]

In Medan, North Sumatera, Indonesia, in school-aged children suspected to have allergies based on symptoms and atopy risk detection cards

from the IPS, there was a significant association between the number of siblings and a positive SPT result (confirmed atopic allergy).[26] However, we did not found a significant association between atopic allergy in infants (as indicated by allergy symptoms and a positive SPT) with maternal parity. Both the Medan study and our study used the same methods to detect allergy symptoms: a modified questionnaire based on the ISAAC criteria and the Hanifin-Rajka allergy detection tool.[26]

The results of the above studies can explain the development of immunotolerance in pregnant women, allowing the emergence of cytokines IL-10 and TGF-β which suppresses excessive immune response. The TGF-β also facilitates the IgA-class switching mechanism of B cells.[5,6,27]

A limitation of the study was the lack of direct measurement of cytokine levels in mothers and their babies, including regulatory cytokines (IL-10, TGF-β), Th1 proinflammatory cytokines (IFN-γ, TNF-α), and Treg populations. A more in-depth study is needed on the effects of harmful substances such as cigarette smoke, heavy metals, and pollutants on the production of human milk and their impact on the immune system of newborns.

In conclusion, secretory IgA in human milk is a complex component that plays a role in the development of infant immunity from early life. Mothers with a history of atopic allergy and frequent infections have higher colostrum sIgA levels. Breastmilk sIgA levels are not associated with allergies in the infant. Maternal exposure to antigens in the form of commensal microbes, pathogens, food, allergens, and air pollutants may stimulate the production of specific breastmilk sIgA.

Conflict of interest

None declared.

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