The primiparous IgA and IL-5 colostrum concentration based on maternal factor: corroborate the inflammation pathways to IgA colostrum synthesis

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BACKGROUND: Immunoglobulin A (IgA) plays a crucial role in the maturation the neonatal mucosal barrier. The accumulation of IgA antibody-secreting cells (ASCs) in the lactating mammary gland facilitates the secretion of IgA antibodies into milk, which are then passively to the suckling newborn, providing transient immune protection against gastrointestinal pathogens. Physiologically, full-term infants are unable to produce IgA, required for mucosal barrier maturation for at least 10 days after birth. Prior studies declare that interleukin 5 (IL-5) responsible to encourage of IgA-producing B cells maturation during lactating periods.
OBJECTIVE: This purpose of this study was determine IgA and IL-5 colostrum concentration based on maternal factors.
STUDY DESIGN: Ninety primiparous with full-term pregnancy and vaginal delivery were enrolled in a cross-sectional study. Colostrum samples were collected on the first day after delivery, followed by the measurement of IgA and IL-5 concentrations using ELISA. Sociodemographic and maternal factors were recorded based on participants' self-reports using a questionnaire.
RESULT: The results showed that mean of colostrum IgA concentration in primiparous 24.9 ± 0.3 years old (95%CI: 24.3–25.6) was 1.51 ± 0.15μg/mL, while colostrum IL-5 concentration was 82.37 ± 20.2pg/mL. The results showed that IgA levels were not significantly correlated with age, education, occupation, weight, height, body mass index (BMI), fish consumption, or smoking habits but were significantly related to baby sex disappointment and weight gain during pregnancy (P<.05). Meanwhile, the IL-5 concentration was significantly correlated with smoking habits, baby's birth weight, and maternal age.
CONCLUSION: The composition of IgA and IL-5 in breast milk is strongly associated with several maternal factors including baby sex disappointment, weight gain during pregnancy, smoking habits, baby's birth weight, and maternal age. This maternal factor corroborate the recently evidence refer to inflammatory pathways involvement in colostrum IgA synthesis.

Key words: Colostrum, IgA, IL-5, primiparous, sociodemographic factor, maternal response, lactating periods, breastfeeding

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Tweetable steatment: Lactation is an important process to provide optimal nutrition and immunological support to infants, especially during the first few months of life. One of the maternal supports by breastfeeding is the transfer of IgA, an immunoglobulin which is important for the maturation of the mucosal barrier of the neonate's respiratory and gastrointestinal tract. This study presents variations in IgA and IL5 levels of primiparous colostrum based on age, education, occupation, height, weight, body mass index, weight gain during pregnancy, smoking habits, frequency of fish consumption in a week, neonatal birth weight, and disappointment with fetal gender. A cross-sectional study involving 90 postpartum mothers showed that several maternal factors including: age, smoking habits before and during pregnancy, neonatal birth weight, baby sex disappointment and weight gain during pregnancy had a significant effect on colostrum IL-5 and IgA concentrations. In the discussion, we discuss the relationship between maternal adaptation related to several of these factors with the conclusion that maternal factors possessed by postpartum mothers are likely to mediate changes in cellular and molecular components that adapt to the nutritional needs of the baby during the lactation period.

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Why this study conducted?

In the first 10 days after birth, infants cannot produce Immunoglobulin A (IgA) in sufficient quantities, the reason they become a vulnerable population to infections. IgA is one type of antibody that plays an important role in protecting the body's mucous membranes from infection, such as in the digestive tract, respiratory tract. During this period, breast milk acts as the main source of IgA for infants, especially colostrum (the first milk produced immediately after birth) contains high concentrations of IgA. Understanding the various maternal factors that may affect colostrum IgA is important to recognize mothers with low colostrum IgA for further management.

Key findings

IL-5 colostrum concentration significantly correlate with maternal age, smoking habits before and during pregnancy, and neonatal birth weight in primiparous mothers. Furthermore, this research also suggests that there was a significant relationship between colostrum IgA concentration with baby sex disappointment and weight gain during pregnancy. Nevertheless, there was no significant correlation between colostrum IL-5 and IgA concentration in this study.

What does this add what is known?

Several studies have shown that maternal obesity can reduce IgA levels in colostrum. Although there was no significant correlation between BMI and colostrum IgA concentration in this study, our study showed that mothers with higher BMI had higher colostrum IgA levels. Previous studies reported that systemic inflammation due to obesity or anxiety affects IgA production by plasma cells in the mammary gland. Ultimately, this study describes maternal adaptation related to maternal factors that affect the immunomodulatory profile of primiparous colostrum.

Introduction

In addition to elderly and immunocompromised cases, newborns are most vulnerable to infection due to immune systems immaturity, particularly 100 days after birth.[1,2] An immature mucosal barrier, as a defense layer primed against pathogen invasion is an established factor that associated with an elevated susceptibility of newborn inflammatory respiratory and gastrointestinal disease.[1] Globally 2.3 million children died in the first month of life in 2020, approximately 6,400 newborn deaths every day.[2] Indonesia is among the 10 countries with the highest number of newborn deaths in 2020 with an estimated 56% caused by unknown etiology, intrapartum complications (31%), complications of prematurity (28%), infections (17%), respiratory problems (11%), and congenital abnormalities (8%).[3,4] Newborns fight against infection immediately after birth is mostly due to lack of postnatal care and delivery complications other than prolonged labor that is significantly associated with increased risk of neonatal death.[5]

It has been established that newborn infants acquire primary immune support from their mothers during pregnancy and breastfeeding. Maternal immunoglobulin (Ig), predominantly immunoglobulin G (IgG), is transferred through the placenta during the 13 week of gestation, even though the level of IgG in fetal circulation is relatively low at approximately 5−10% of maternal levels and subsequently tends to increase at the end of pregnancy. Several prior studies reported that maternal immunoglobulins are suitable for fetal protection before the maturation of the immune system. Appropriate nutritional intake after birth is important for neonatal growth and maturation of the immune system. Maternal milk contains abundant bioactive compounds, including IgA, which is considered the gold standard of neonatal nutrition for protection against respiratory tract and gastrointestinal infections. Physiologically, a full-term infant undergoes IgA deficiency for at least 10 days after birth, highlighting the importance of maternal Ig transfer for stimulating maturation of the neonatal mucosal barrier.[6−8]

Human milk produced by the mammary glands 2−4 days after delivery, called colostrum (300−400 mL/day), contains higher levels of proteins such as Ig, lower levels of carbohydrates, and higher fat content than mature milk. A previous study reported that IgA concentration in colostrum is 88−90% higher than that in mature milk.[8,9] Immunoglobulin A has multiple features and functions to encourage optimal maturation of the mucosal barrier defense system by neutralizing pathogens before adhering to epithelial cells and preventing excessive inflammation or tissue damage.[10−12] Breastmilk IgA production is mainly controlled by transforming growth factor (TGF)-β and several cytokines produced by Th2 cells, including interleukin 4 (IL-4), IL-5, IL-6, IL-10, and IL-21.[13−16] Previous studies have reported that IL-5 promotes B cell maturation into IgA-secreting cells.[17,18]

Earlier investigations have highlighted the importance of maternal and environmental factors influencing breast milk composition, such as mode of delivery, diet, parity, BMI, and psychological status.[10,11] A clear understanding of the various maternal factors that influence colostrum IgA production is an important step in designing strategies and interventions to improve maternal and fetal health in early life. Therefore, this study aimed to determine the pattern of IgA and IL5 in primiparous colostrum in relation to maternal factors.

Material and methods

Study design

This population-based cross-sectional study was conducted in Giayar Bali, Indonesia.

Participant

The preliminary study was conducted at the Gianyar mother and child polyclinic showed that the number of primiparous with vaginal delivery without

complications during the period from October to December 2022 was 109 womans, so if calculated according to the Slovin formula, with a significance level of 5%, the number of samples obtained was 86 women. The research subject recruitment process begins by providing the research aim and procedures carried out by the principal investigator and trained assistant, using predetermined eligibility criteria. Primiparous women without pregnancy or delivery complications in the Gianyar Regency, Bali, from February to April 2023 were involved in this project. Nonprobability purposive sampling was performed to select primiparous mothers with full-term pregnancy, first day postpartum, vaginal delivery without complications such as obstructed labor, forceps, vacuum, babies born in a healthy condition without congenital abnormalities, and signed informed consent to participate in this study. Women who were multiparous and had a history of hypertension, diabetes, obesity, HIV, allergies, asthma, rheumatoid arthritis, gastritis, and Hodgkin's disease, which can affect IgA levels in breast milk, were excluded. The investigation and sample collections was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of The Health Research Ethics Commission (HREC) of the Faculty of Medicine and Health Science of Universitas Warmadewa with Ethical Clearance Certificate Number: 293/Unwar/FKIK/ECKEPK/I/2023, on 28 January 2023.

Sociodemographic and clinical measures

Sociodemographic factors included age, employment, education, weight gain during pregnancy, body mass index, newborn weight, smoking habits, fish consumption per week, and gender disappointment. Mothers were asked to complete self-report questionnaires regarding their subjective smoking habits before and during pregnancy, fish consumption per week, and sex disappointment after antenatal ultrasound examination. Their medical records, including weight, height, and newborn weight, were also recorded.

Sample collection and measurement

Breast milk on the first postpartum day was collected in a private room, preceded by 15 min of breast massage and care by the professional midwife. After centrifuged at 800 × g for 10 min at 40° C breast milk samples were placed in 2.5 mL Eppendorf tubes and stored at −20°C until assay with an ELISA reader. IL-5 expression was examined using human IL-5 (ab. 100571) and IgA using a human IgA ELISA Kit (cat. no. KA3980 Abnova) based on manufacturer's instructions.

Data analysis

The results of the statistical analyses are presented as mean values and standard deviations (SD) for numerical data, Meanwhile, categorical data is presented in numbers and percentages. Normality was testing using Kolmogorov-smirnov test. Logistic and linier regression was performed to answer our hypotheses. All data analyses were performed using STATA 18 software, *P* values less than .05, were considered statistically significant.

Results

In this study, we investigated colostrum IgA and IL-5 levels in primiparous mothers. The average age was 24.9 years (SD=0.3). In total, 65.5% of the participants declared that they had a senior high school education, 16.7% declared that they had a diploma education, 70% worked full-time, and 30% were housewives. The average mother's weight was 64.1 kg (SD=0.5), with an average height of 160.2 cm (SD=0.6). Furthermore, 65.6% of the women had a normal BMI, 32.2% were overweight, and 2.2% had obesity type I, with an average weight gain during pregnancy was 13.4 kg (SD=0.3). The majority of participants (94.4%) declared having no smoking habits before or during pregnancy, and at least 5.6% stated that they had a habit of smoking before and during pregnancy. Most participants (92.2%) reported consuming fish more than three times a week during pregnancy and 7.8% reported consuming fish less than three times a week during pregnancy. The average weight of a newborn baby was 3264.7 g (SD=22.5). In addition, 10% of the women declared disappointment with the baby's sex after antenatal ultrasound examination, and most (90%) did not declare disappointment with the baby's sex after antenatal ultrasound examination. The detailed participant characteristics are summarized in Table.

The results of the analysis showed that the mean IgA colostrum concentration in primiparous was 1.51 ± 0.15 μg/mL, while the mean level of IL-5 colostrum concentration was 82.37 ± 20.2 pg/mL. There was no significant correlation between IL-5 and IgA levels in primiparous colostrum (*P*=.546). Furthermore, the influence of maternal characteristics, including age, education, occupation, BMI, smoking habits, sex rejection, and fish consumption, was analyzed in detail. The correlations between these values and the maternal characteristics are presented in Table. The results showed that colostrum IgA concentration was not significantly correlated with maternal age, education, occupation, weight, height, BMI, fish consumption, and smoking habits but was significantly related to baby sex disappointment and weight gain during pregnancy (*P*<.05). Meanwhile, the IL-5 colostrum concentration was significantly correlated with smoking habits, newborn baby weight, and maternal age.

Comment

Principal findings

Our findings suggest that there is no positive association between IgA colostrum level and IL5 primiparous colostrum concentration. Nevertheless, this study outcome indicate that several maternal factor including baby sex disappointment and weight gain during pregnancy were significantly correlated with IgA colostrum concentration, while IL-5 colostrum concentrations in primiparous women were significantly correlated with newborn weight, maternal age, and smoking habits before and during pregnancy. Women with obesity, smoking habits, anxiety regarding the baby's gender, and private employees showed a trend in colostrum IgA levels

TABLE
Immunomodulatory profile based on maternal basic characteristics

Parameter	Mean ± SD (n=90)	95%CI	Colostrum profile			
			IL-5 (pg/mL)	*P* value	IgA (μg/mL)	*P* value
Age (years)	24.9 ± 0.3	24.32–25.58		.003[a]		.584
Education, n (%)						
Senior High School	59 (65.5)		63.05 ± 26.1		1.40 ± 0.2	
Diploma	15 (16.7)		162.70 ± 46.5	.323	2.37 ± 0.4	.796
Bachelor	16 (17.8)		93.56 ± 30.7		1.23 ± 0.4	
Job, n (%)						
Housewife	27 (30)		72.66 ± 38.8		1.46 ± 0.3	
Teacher	2 (2.2)		96.71 ± 34.9	.925	1.22 ± 0.2	.273
Private-employed	45 (50)		83.77 ± 30.07		2.01 ± 0.3	
Self-employed	16 (17.8)		26.64 ± 0.6		1.31 ± 0.1	
Weight (kg)	65.5 ± 0.5	64.37–66.59		.605		.422
Height (cm)	161.4 ± 0.6	160.28–162.53		.431		.239
BMI, n(%)						
Underweight	0		0		0	
Normal	59 (65.6)		82.54 ± 33.9	.917	1.55 ± 0.2	.765
Overweight	29 (32.2)		84.49 ± 20.9		1.32 ± 0.2	
Obese type I	2 (2.2)		38.15 ± 0.2		4.41 ± 0.2	
Weight gain (kg)	13.4 ± 0.3	12.82–13.86		.505		.008[a]
Smoking						
Yes	5 (5.6)		400.83 ± 209.4	.000[a]	2.57 ± 1.1	.113
No	85 (94.4)		66.44 ± 17.1		1.46 ± 0.1	
Fish consumption						
≤3× a week	7 (7.8)		3.88 ± 6.2	.759	1.21 ± 0.1	.710
>3× a week	83 (92.2)		6.68 ± 2.9		1.53 ± 0.2	
Baby's newborn weight (g)	3264.7 ± 22.5	3248.26–3350.79		.036[a]		.246
Baby sex disappointment						
Yes	9 (10)		104.78 ± 38.7	.620	2.25 ± 0.3	.025[a]
No	81 (90)		77.88 ± 22.8		1.36 ± 0.2	

BMI, body mass index; *CI*, confident intervals; *cm*, centimeters; g, grams; *IgA*, Immunoglobulin A; *IL-5*, Interleukin 5; *kg*, kilograms; *mL*, mililiter; *pg*, picogram; *SD*, standart deviation; *μg*, microgram.

[a] *P* values less than .05.

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which tended to be higher, although it was not statistically significant.

Result in the context of what is know

The vulnerability of newborns can be overcome by the transplacental transfer of pathogen-specific antibodies and other immune mediators from the mother during pregnancy, followed by immune support through exclusive breastfeeding, particularly colostrum. Evidence shows that breast milk antibodies are major contributors to improving a baby's immune defense against infection.[19] It has been revealed that parity influences IgA levels in both colostrum and breast milk, multiparous mothers have lower IgA levels compared to primiparous mothers. Women who underwent delivery by cesarean section showed higher maternal IgA colostrum concentrations than the vaginal delivery.[20,21] Likewise, it was reported that the early IgA concentration was higher in prematurely than full-term pregnancy.[22,23] Based on this report, to minimize variations in IgA and IL-5 colostrum concentration measurement, this study focused on selecting primiparous women with full-term pregnancy and vaginal delivery.

As mentioned, postbirth conditions may be associated with a shift in immunoglobulin levels, which can be affected by various factors.[24−29] This study confirmed that concentrations of IL-5 colostrum were higher in primiparous women who declared their smoking habits before and during pregnancy. Widespread knowledge of environmental tobacco smoke (ETS) exposure has been linked to various health impacts, including pregnancy, by mediating the secretion of inflammatory factors and promoting the occurrence of inflammation.[30−32] Nevertheless, a previous study showed that IL-1β and IL-8 levels were significantly lower in colostrum, and IL-6 levels were significantly lower in the mature milk of smoking mothers. Moreover, maternal smoking did not have a significant impact on IL-2, IL-4, IL-5, IL-10, IFN-γ, TNF-α, or TNF-β breast milk concentrations.[33]

Extending our discovery regarding a significant correlation between IL-5 colostrum concentration and maternal age, other studies suggest that IL-1β and IL-6 concentrations are higher in the colostrum of older mothers (>35 years) compared with adolescent mothers (<24 years), while the levels of IL-8 and TNFα did not differ in the three groups including pregnant women aged 24−35 years.[34] Corroborating this statement, other research findings show a significant association between maternal age and colostrum TGF-β levels, possibly related to increased oxidative stress during breastfeeding in older mothers.[35,36] Conversely, babies with low birth weight or due to prematurity have higher concentrations of chemokines and cytokines in both colostrum and mature milk than full-term babies who have normal birth weight.[37] The involvement of cytokines in the stimulation of prostaglandin production is widely accepted. Prostaglandins mediate softening of the cervix and stimulate uterine contractions that predominate in the fundus and lead to initiation of preterm birth.[38,39]

The role of cytokines in IgA synthesis has been described in several studies. Physiologically, TGF-β and IL-5 increase in the mammary gland during lactation and contribute to IgA synthesis in breast milk.[40−42] Our results did not show a significant correlation between IgA and IL-5 in primiparous colostrum; indeed, it is likely that several types of cytokines in colostrum may affect their correlation. However, the relevance of colostrum IgA to maternal weight gain and obesity remains unclear. Obesity induces massive inflammation and oxidative stress possibly affecting the composition of breast milk including IgA due to changes in metabolic hormones and insulin resistance.[43] In our study, we observed IgA colostrum concentration was significantly related to weight gain during pregnancy. In addition, our results may reflect those of Fujimori et al, who reported that colostrum IgA and serum IgA concentrations were significantly higher in overweight and obese mothers.[44] Maternal disappointment with the fetal sex may affect positive or negative attitudes during lactation. Several studies have shown that pregnant women have increased serum levels of pro-inflammatory cytokines as acute-phase proteins relevant to anxiety-related disorders.[45−47] Our study showed that mothers who declared a baby sex disappointment had higher IL-5 colostrum levels, although this was not statistically significant, but they showed significantly higher IgA levels. These findings are in contrast to a prior investigation that demonstrated that maternal anxiety was negatively associated with milk IgA levels.[48,49]

Clinical implications

The results of our research show that mothers who are experiencing systemic inflammatory conditions due to obesity, smoking habits or anxiety need to continue breastfeeding neonates to support the maturation of the baby's immune system, especially the development of the gastrointestinal and respiratory mycosal barriers. It can be concluded that breast milk is the best food for neonates even though the mother has a nonphysiological condition, the nutrient composition in breast milk will still be adapted to the maternal condition and the needs of immunomodulators for the development of the neonate. Obese women, or have a smoking habit or experience anxiety due to dissatisfaction with the gender of the fetus have been proven to show higher levels of colostrum IgA so there is no reason for a mother to stop breastfeeding, especially during the colostrum period.

Research implications

These findings extends the prior concept which states that inflammation related factors are contributors to colostrum IgA synthesis, however several mediators such as the involvement of CCL28 and miR200a need to be validated to prove the relationship between alveolar size and IgA synthesis. In addition, the effect of excessive exposure to inflammatory cytokines in obese mothers or mothers who experience anxiety on the maturation of the baby's mucosal barrier needs to be studied further, whether it inline with the incidence of gastrointestinal and respiratory infections in neonates or not.

Strengths and limitations

Our results have extended the knowledge regarding IgA colostrum composition and and IL-5 levels in healthy primiparous individuals. This research provides a better understanding of how these factors can influence the composition of IgA given to babies through colostrum, and can be used as a basis for identifying strategic steps that can improve the quality and benefits of breast milk for baby health.

A limitation of our study is that disappointment in baby sex was self-reported by a questionnaire that did not entirely represent maternal anxiety; subsequently, no biological stress markers were included. Second, our analysis covered only a few colostrum biological markers; therefore, the results may not be generalizable to all immunological factors, and there are still many maternal factors that have not been validated in this study, such as a history of allergies or eating habits of junk food, which may influence colostrum IL-5 and IgA levels. Third, the outcomes were limited to one time point (maternal colostrum profile

regarding IgA and IL-5 levels was measured only during the first days after delivery). Follow-up points of maternal colostrum IgA and its social predictors could show the variation in IgA and Il-5 levels over time, as well as establish whether there is a risk for sustaining the relationship between variables in this study. Additional studies with larger sample sizes and diverse groups, especially primiparous individuals with different smoking habits, are needed to better understand how IL-5, other proinflammatory cytokines, and IgA are produced and modified under different environmental and maternal physiological conditions

Conclusion

Critical results were achieved in at least three main aspects. These findings confirmed the absence of a significant relationship between colostrum IgA and IL-5 levels in primiparous women. Second, there was a significant relationship between IL-5 colostrum concentration and maternal age, smoking habits before and during pregnancy, and birth weight in primiparous mothers. Third, this research suggests that there is a significant relationship between colostrum IgA concentration and baby sex disappointment and weight gain during pregnancy. Owing to the limitations mentioned above, these outcomes should be interpreted with caution. ■

CRediT authorship contribution statement

Kadek A. Kurniawan: Project administration, Investigation, Funding acquisition, Conceptualization. **Sri Winarsih:** Supervision, Methodology, Conceptualization. **Nurdiana Nurdiana:** Supervision, Conceptualization. **Sri Andarini:** Supervision, Conceptualization. **Wiwit Nurwidyaningtyas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. ■

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