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Original Article

Supplementation of 2'-Fucosyllactose in Formula-Fed Infants Has Potential Benefits to Reduce the Risks of Infantile Colic and Atopic Dermatitis in Infancy

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ABSTRACT

Purpose: Human milk oligosaccharides (HMOs) are non-digestible carbohydrates found in breast milk, with 2'-fucosyllactose (2'-FL) being a prominent type. This study examined the effects of HMOs on the incidence of infantile colic (IC) and atopic dermatitis (AD) in full-term infants who were breastfed (BM), formula-fed (FF), or fed formula supplemented with 2'-fucosyllactose (FF_2'-FL) for 1 year.
Methods: This open-label, prospective clinical trial enrolled 338 full-term infants from 2020 to 2024. IC was diagnosed using the ROME IV criteria, and AD was assessed with the PO-SCORAD.The study evaluated the incidence of IC and AD, infant growth, and risk factors for IC and AD.
Results: A total of 113 infants were in the BM group, 111 in the FF group, and 114 in the FF_2'-FL group. Maternal baseline characteristics, including delivery age (p=0.001) and delivery type (p=0.013), differed significantly among the three groups. The incidence of IC in the FF_2'-FL group was comparable to that in the BM group (10.5% vs. 8.8%; odds ratio [OR], 1.21; 95% confidence interval [CI], 0.501-2.929; p=0.795) and lower than in the FF group (10.5% vs. 15.3%, OR, 0.65; 95% CI, 0.295-1.434; p=0.120). Similarly, the incidence of AD in the FF_2'-FL group was close to that in the BM group and lower than in the FF group.
Conclusion: This study suggests that supplementation with 2'-fucosyllactose may help reduce the risk of IC and AD. These findings have important implications for pediatric healthcare and support the development of preventive strategies for IC and AD beyond breastfeeding.

Keywords: Breast milk; Colic; Oligosaccharides

INTRODUCTION

Human milk oligosaccharides (HMOs) are a class of non-digestible carbohydrates abundant in human milk, ranking as the third most prevalent solid constituent after lactose and lipids [1]. The HMO composition in human milk varies significantly, influenced by factors such as maternal genetics [2], lactation stage [3], and geographic location [4]. The structural

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Conflict of Interest

The authors have no financial conflicts of interest.

heterogeneity of HMOs enables functional synergy across categories, as they collectively support digestive health, enhance immune system development, and contribute to cognitive function in infants [1]. Over 100 distinct HMOs have been identified in breast milk [5], with 2'-fucosyllactose (2'-FL) [6], among the most extensively studied due to its promising role in infant nutrition [7]. 2'-FL, the most abundant HMO, accounts for nearly 30% of total HMOs in secretor mothers and serves as a major carbohydrate substrate [7]. It also inhibits *Campylobacter jejuni* colonization and associated mucosal inflammation, enhances neurodevelopmental outcomes, and improves learning and memory performance [7].

Atopic dermatitis (AD) is a prevalent allergic skin disorder with rising incidence during early childhood, representing a major public health burden in developed regions. In Taiwan, the prevalence of AD among schoolchildren aged 6-7 years reached 29.8% in 2007 [8], and 5.9% of children under 2 years had a physician-confirmed diagnosis. The growing prevalence of AD [9] highlights the importance of understanding its etiological pathways and advancing preventive strategies. Several studies have shown that breastfeeding modulates gut microbiome composition and may reduce the risk of developing AD [10,11]. These findings point to the role of bioactive milk components such as HMOs in protecting against childhood AD through microbiota-mediated immune regulation [12,13]. Exclusive breastfeeding during the first three months of life is associated with a reduced incidence of AD in children with a family history of atopy [14]. Among individuals with AD, reduced diversity and depletion of specific bacterial taxa in the gut microbiota have been observed, supporting the rationale for probiotic-based interventions in pediatric AD prevention and management [15].

Breastfeeding and probiotics have also been shown to reduce the incidence of infantile colic (IC), a distressing condition characterized by prolonged episodes of crying, restlessness, or irritability in infants without an identifiable cause [16]. The global incidence of IC ranges from 10% to 40% [17,18], and studies consistently report a lower incidence of IC among breastfed infants compared to those who are formula-fed [19]. Although the precise etiology of IC remains unclear, significant differences in intrapartum antibiotic exposure and breastfeeding rates have been observed between infants with and without colic [20]. In a recent randomized trial, infants whose mothers consumed Actiregularis demonstrated reduced crying frequency and intensity [21]. This had a positive impact on breastfeeding outcomes and growth indicators, supporting the hypothesis that enhancing gut microbiota may reduce the risk of IC [21]. These findings underscore a close association between early gut microbiota composition and the development of IC. Research has shown that IC is associated with gut inflammation, as evidenced by elevated fecal calprotectin levels, and gut dysbiosis, independent of feeding type [22].

Given these insights, this study examines the additional benefit of HMO-supplemented formula specifically 2'-fucosyllactose compared to standard formula feeding, in preventing infantile colic and AD through modulation of gut inflammation and immune responses. Infants in the breastfed group serve as the reference for between-group comparisons.

MATERIALS AND METHODS

Study design

This was a single-center, prospective, open-label clinical trial conducted at National Cheng Kung University Hospital (NCKUH). The study enrolled full-term infants with an uneventful

perinatal course from 2020 to 2024 and assigned them to one of three feeding groups after obtaining the written informed consents from their parents. The study protocol was reviewed and approved by the Institutional Review Board of NCKUH (No. A-BR-109-005).

Inclusion and exclusion criteria of subjects

All enrolled infants met the inclusion criteria: full-term infants (gestational age ≥37 weeks) with birth weights between 2,500 g and 4,000 g, delivered at NCKUH or the Fu-A-An Women & Children Clinic. Infants were excluded if they met any of the following criteria: perinatal insults, maternal antimicrobial use within one month prior to delivery, congenital abnormalities affecting growth, or major illnesses requiring Level II or neonatal intensive care unit admission.

Allocation of groups

Eligible infants were assigned to one of three feeding groups. Infants exclusively fed breast milk (BM) for at least 4 months were classified as the BM group. Infants fed with standard formula for 6 months (either fully or partially, with BM constituting less than 20% of total intake) were classified as the Formula-Fed (FF) group. Infants fed formula supplemented with 2'-FL were classified as the FF_2'-FL group. Informed consent was obtained from all participating mothers.

Records of demographics and follow-ups

Eligible infants were regularly followed up at birth and at weeks 4, 8, 16, 24, and 52 after delivery. Data collected included body weight, height, head circumference, presence of crying, restlessness or irritability, symptom duration, fever, skin lesions, and other illnesses. Infantile colic was diagnosed using the ROME IV criteria, and AD was assessed with the patient oriented-scoring atopic dermatitis (PO-SCORAD) scoring system. The PO-SCORAD questionnaire, which evaluates AD characteristics, was completed by caregivers with assistance during each visit for vaccination or healthcare.

Statistical analysis

We compared the incidence of infantile colic and AD in infants before 5 months of age and at one year of age, respectively. Normality tests were conducted to assess the distribution of continuous variables. Summary statistics included the mean with standard deviation (SD) for normally distributed variables, and the median with interquartile range (interquartile range) for non-normally distributed variables. Categorical variables were summarized using frequencies and proportions. Between-group comparisons for continuous variables were performed using *t*-tests for normally distributed data and Mann–Whitney U-tests for non-normally distributed data. Categorical variables were compared using chi-squared tests or Fisher's exact tests, as appropriate. Potential risk factors were first evaluated using univariate logistic regression. Multivariate logistic regression was then performed, including predictor variables with *p*-values less than 0.2. A parsimonious multivariate model was subsequently constructed using a stepwise selection approach.

RESULTS

Participants and grouping

A total of 338 infants were enrolled, with 113 infants in the BM group, 111 in the FF group, and 114 in the FF_2'-FL group (**Fig. 1A**).

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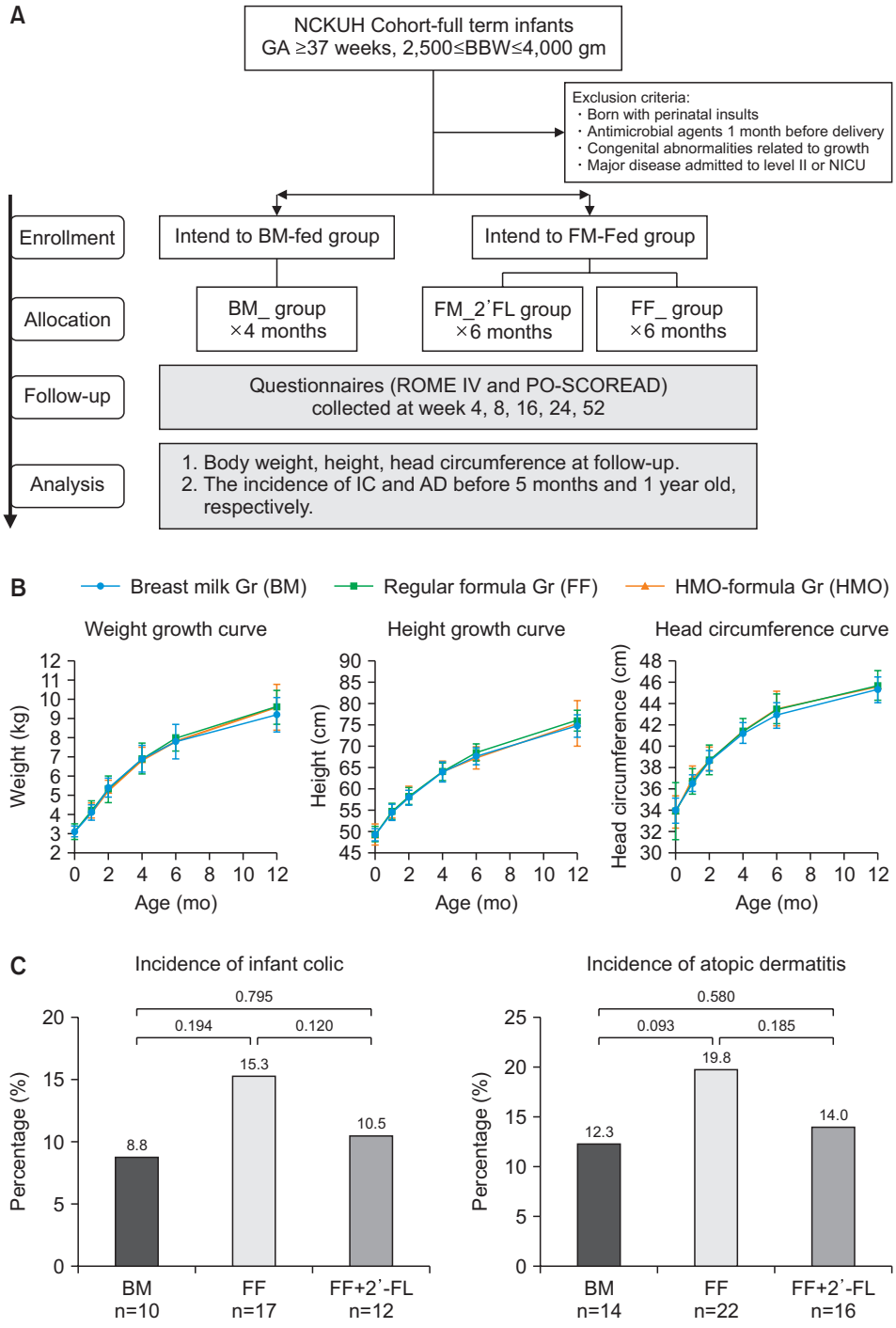

Fig. 1. (A) Flow diagram of the clinical study design. (B) Serial measurements of weight, height, and head circumference in infants fed with breast milk, standard FF, and formula supplemented with 2'-FL over one year. (C) Incidence of infantile colic (IC) and AD in infants across different feeding modes.
FF: formula, AD: atopic dermatitis, IC: infantile colic, GA: gestational age, BBW: birth body weight, FM: formulafed, PO-SCOREAD: patient oriented-scoring atopic dermatitis. NCKUH: National Cheng Kung University Hospital, NICU: neonatal intensive care unit, BM: breastfed.

Demographic characteristics of mothers and infants across the three groups

Table 1 presents the demographic characteristics of mother–infant pairs across the three feeding groups. Maternal delivery age and rate of normal spontaneous delivery differed

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Table 1. Baseline characteristics of enrolled mothers and their infants grouped by feeding type

Characteristics	BM (n=113)	FF (n=111)	FF + 2'-FL (n=114)	*p*-value*		
				BM vs. FF	BM vs. FF + 2'-FL	FF vs. FF + 2'-FL
Mom's factors						
Age of delivery (y)	33.7±4.6	31.6±4.7	31.9±5.0	0.001	0.007	>0.999
>1 parity	62 (54.9)	49 (44.1)	63 (55.3)	0.098		
Blood type				0.687		
A	21	23	20			
B	36	41	34			
AB	10	10	6			
O	46	37	44			
Probiotics used during pregnancy	10 (8.8)	22 (19.8)	20 (17.5)	0.055		
Parents' allergy history	6 (5.3)	4 (3.6)	4 (3.5)	0.747		
Infant's factors						
Female	63 (55.7)	53 (47.7)	52 (45.6)	0.274		
Gestational age (wk)	38.5±0.9	38.9±1.0	38.9±0.9	0.083		
NSD	59 (52.2)	70 (63.0)	81 (71.1)	0.013	0.004	0.20
Baby's probiotics used	22 (19.5)	25 (22.5)	13 (11.4)	0.109		
Birth body weight (gm)	3,069.7±304.0	3,138.0±359.3	3,106.9±353.3	0.632		
Birth body height (cm)	48.6±1.4	49.3±1.8	49.2±2.3	0.942		
Birth head circumference (cm)	33.5±1.2	34.0±2.7	33.8±1.4	0.99		

Values are presented as mean±standard deviation, number (%), or number only.
BM: breastfed, FF: formula-fed, FF_2'-FL: formula-fed with 2'-FL supplement, NSD: normal spontaneous delivery.
*Between-group comparisons of continuous variables were conducted using *t*-tests or Mann–Whitney U-tests, and categorical variables were compared using chi-squared tests or Fisher's exact tests.

significantly among the groups, with *p*-values of 0.001 and 0.013, respectively. Post hoc analysis showed that mothers in the BM group had significantly higher delivery ages than those in the FF group (33.7 vs. 31.6 years, $p=0.001$) and the FF_2'-FL group (33.7 vs. 31.9 years, $p=0.007$). Additionally, mothers in the FF_2'-FL group had a significantly higher rate of normal spontaneous delivery than those in the BM group (71.1% vs. 52.2%, $p=0.004$). Other variables, including parity, maternal blood type, probiotic use during pregnancy, maternal allergy history, infant sex, gestational age, probiotic use, birth weight, height, and head circumference, did not differ significantly among the groups (all $p>0.05$).

The body weight, height, and head circumference of infants at each follow-up between groups

Fig. 1B shows the growth curves for body weight, height, and head circumference of infants from birth to one year of age across the three groups. At the end of the follow-up (one year), mean body weight, body length, and head circumference were not significantly different between groups at any study visit (all $p>0.05$). After one year of feeding, the mean body weight (±SD) was 9.3±1.3, 9.6±0.93, and 9.5±1.11 kg in the BM, FF, and FF_2'-FL groups, respectively. The mean body height was 73.2±1.5, 76.0±2.4, and 75.3±4.9 cm in the BM, FF, and FF_2'-FL groups, respectively. Head circumference was 44.5±1.1, 45.7±1.4, and 45.8±1.3 cm in the three groups, respectively. Overall, there were no notable differences among the groups in any growth parameters.

The incidence and relative risks of IC and AD development between infants with different feeding types

The incidence of IC before 5 months of age and AD from birth to one year of age are presented in **Fig. 1C** and **Table 2**. The incidence of IC in the FF_2'-FL group was comparable to that of the BM group (10.5% vs. 8.8%; odds ratio [OR], 1.21; 95% confidence interval [CI], 0.501–2.929; $p=0.795$) and lower than that of the FF group (10.5% vs. 15.3%; OR, 0.65; 95% CI, 0.295–1.434; $p=0.120$). Similarly, the incidence of AD in the FF_2'-FL group followed

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Table 2. Pairwise comparison of the incidence of infantile colic and atopic dermatitis among infants fed using different feeding methods

A

Feeding types, n/N (%)	Incidence of IC	OR (95% CI)	*p*-value
BM vs. FF	10/113 (8.8) vs. 17/111 (15.3)	1.86 (0.813–4.270)	0.194
FF vs. FF_2'-FL	17/111 (15.3) vs. 12/114 (10.5)	0.65 (0.295–1.434)	0.120
BM vs. FF_2'-FL	10/113 (8.8) vs. 12/114 (10.5)	1.21 (0.501–2.929)	0.795
Total	39/338 (11.5)		

B

Feeding types, n/N (%)	Incidence of AD	OR (95% CI)	*p*-value
BM vs. FF	14/113 (12.3) vs. 22/111 (19.8)	1.75 (0.843–3.622)	0.093
FF vs. FF_2'-FL	22/111 (19.8) vs. 16/114 (14.0)	0.66 (0.326–1.337)	0.185
BM vs. FF_2'-FL	14/113 (12.3) vs. 16/114 (14.0)	1.16 (0.535–2.493)	0.580
Total	52/338 (15.4)		

n/N (%): number of infants with events/number of infants per group, OR: odds ratio, CI: confidence interval, BM: breastfed, FF: formula-fed, FF_2'-FL: formula-fed with 2'-FL supplement, IC: infantile colic, AD: atopic dermatitis.

the same trend as IC, being similar to the BM group (14.0% vs. 12.3%; OR, 1.16; 95% CI, 0.535–2.493; p=0.580) and lower than the FF group (14.0% vs. 19.8%; OR, 0.66; 95% CI, 0.326–1.337; p=0.185).

The risk factors of IC and AD

The risk factors for IC and AD in this cohort of full-term infants are summarized in **Table 3**. Maternal allergy history was identified as a significant risk factor for both IC (12.8% vs. 1.3%, p<0.001) and AD (9.6% vs. 1.4%, p=0.003) in univariate analysis. Among infant-related variables, antibiotic use showed no statistical significance for either IC (20.5% vs. 10.0%, p= 0.057) or AD (19.2% vs. 9.8%, p=0.052).

Two multivariate logistic regression models were performed:

The first model included variables with a univariate p-value<0.2, namely maternal delivery age, probiotic use during pregnancy, maternal allergy history, maternal health supplement use during pregnancy and breastfeeding, annual household income, infant antibiotic use, birth height, and gestational age.

The second model applied a stepwise selection method.

Both models identified maternal health supplement use during pregnancy as an independent risk factor for IC development (**Table 3A**).

For AD, maternal allergy history remained statistically significant, with 9.6% (n=5/52) of infants in the AD group and 1.4% (n=4/286) in the non-AD group (**Table 3B**). Multivariate analysis using variables with p<0.2, maternal delivery age, probiotic use during pregnancy, maternal allergy history, father's education level, infant sex, antibiotic use, and probiotic use indicated that maternal allergy history was significantly associated with a higher likelihood of AD in infants (OR, 6.49; 95% CI, 1.59–26.52; p=0.009). A stepwise regression model further showed that higher family income and infant probiotic use were associated with increased odds of AD, with ORs of 6.79 (95% CI, 1.35–34.22; p=0.020) and 5.93 (95% CI, 1.01–34.91; p=0.049), respectively.

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Table 3. Univariate and multivariate logistic regression analyses of the risk factors for infantile colic and atopic dermatitis in infants aged <5 months

A

Predictors	Infantile colic (n=39)	Non-infantile colic (n=299)	Univariate model		Multivariate univariate $p<0.2$ in		Multivariate based on stepwise method	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Parental factors								
Age of delivery (y)	33.9±4.8	32.5±4.9	1.06 (0.99, 1.14)	0.104	1.06 (0.89, 1.27)	0.481		
Probiotics used during pregnancy	9 (23.1)	44 (14.7)	1.74 (0.77, 3.91)	0.181	3.66 (0.26, 51.80)	0.337		
Antibiotics use before pregnancy	0 (0.0)	1 (0.3)	0.00 (<0.001, >999.9)	0.992				
Maternal allergy history	5 (12.8)	4 (1.3)	10.84 (2.78, 42.31)	<0.001*	3.30 (0.13, 86.77)	0.474		
Health supplements during pregnancy	11 (28.2)	49 (16.4)	2.00 (0.94, 4.29)	0.074	25.05 (2.61, 239.92)	0.005*	6.83 (1.82, 25.63)	0.004*
Health supplements during breastfeeding	8 (20.5)	31 (10.4)	2.23 (0.94, 5.28)	0.068	0.16 (0.02, 1.57)	0.115		
Gestational diabetes mellitus	0 (0.0)	4 (1.3)	0.00 (<0.001, >999.9)	0.990				
Father smoking	1 (2.6)	4 (1.3)	1.94 (0.21, 17.82)	0.558				
Mother smoking	0 (0.0)	1 (0.3)	0.00 (<0.001, >999.9)	0.992				
Father's education level (> bachelor)	5 (12.8)	27 (9.0)	1.48 (0.53, 4.10)	0.450				
Mother's education level (>bachelor)	5 (12.8)	25 (8.4)	1.61 (0.58, 4.49)	0.361				
Annual household income (>NT$ 1.5 million)	7 (17.9)	97 (32.4)	0.46 (0.19, 1.07)	0.071	0.29 (0.04, 2.03)	0.212		
Lactational mastitis	0 (0.0)	4 (1.3)	0.00 (<0.001, >999.9)	0.990				
Infant's factors								
Sex (female/male)	19/20	151/148	1.07 (0.55, 2.09)	0.834				
Delivery mode (NSD/C-section)	23/16	187/112	1.16 (0.59, 2.29)	0.666				
Birth parity (=1/>1)	18/18	152/142	1.07 (0.54, 2.14)	0.847				
Antibiotics use	8 (20.5)	30 (10.0)	2.31 (0.98, 5.49)	0.057	0.77 (0.09, 6.32)	0.811		
Probiotics used	0 (0.0)	9 (3.0)	0.00 (<0.001, >999.9)	0.984				
Birth body height (cm)	50.1±2.2	49.2±1.6	1.39 (0.96, 2.01)	0.081	1.43 (0.93, 2.20)	0.104		
Gestational age (wk)	38.6±0.9	38.9±0.9	0.73 (0.50, 1.06)	0.102	0.75 (0.28, 2.05)	0.582		
Birth body weigh (gm)	3,088.3±396.2	3,115.5±333.6	1.00 (1.00, 1.00)	0.643				

B

Predictors	Atopic dermatitis (n=52)	Non-atopic dermatitis (n=286)	Univariate model		Multivariate univariate $p<0.2$ in		Multivariate based on stepwise method	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Parental factors								
Age of delivery (y)	33.5±3.9	32.5±5.0	1.04 (0.98, 1.11)	0.173	1.03 (0.96, 1.09)	0.426		
Probiotics used during pregnancy	12 (23.1)	41 (14.3)	1.79 (0.87, 3.70)	0.115	1.56 (0.71, 3.39)	0.266		
Antibiotics use before pregnancy	0 (0.0)	1 (0.3)	0.00 (<0.001, >999.9)	0.991				
Maternal allergy history	5 (9.6)	4 (1.4)	7.50 (1.94, 28.96)	0.003*	6.49 (1.59, 26.52)	0.009*		
Health supplements during pregnancy	10 (19.2)	50 (17.5)	1.12 (0.53, 2.39)	0.762				
Health supplements during breastfeeding	7 (13.5)	32 (11.2)	1.23 (0.51, 2.97)	0.637				
Gestational diabetes mellitus	0 (0.0)	4 (1.4)	0.00 (<0.001, >999.9)	0.988				
Father smoking	1 (1.9)	4 (1.4)	1.38 (0.15, 12.62)	0.774				
Mother smoking	0 (0.0)	1 (0.3)	0.00 (<0.001, >999.9)	0.991				
Father's education level (>bachelor)	8 (15.4)	24 (8.4)	1.98 (0.84, 4.70)	0.119	1.81 (0.73, 4.44)	0.198		
Mother's education level (>bachelor)	7 (13.5)	23 (8.0)	1.78 (0.72, 4.39)	0.211				
Annual household income (>NT$ 1.5 million)	19 (36.5)	85 (29.7)	1.36 (0.73, 2.53)	0.328			6.79 (1.35, 34.22)	0.020*
Lactational mastitis	1 (1.9)	3 (1.0)	1.85 (0.19, 18.13)	0.597				
Infant's factors								
Sex (female/male)	21/31	147/139	0.64 (0.35, 1.17)	0.146	0.72 (0.38, 1.33)	0.293		
Delivery mode (NSD/C-section)	33/19	177/109	0.93 (0.51, 1.73)	0.830				
Birth parity (=1/>1)	25/27	145/133	1.18 (0.65, 2.13)	0.589				
Antibiotics use	10 (19.2)	28 (9.8)	2.19 (0.99, 4.85)	0.052	1.85 (0.80, 4.28)	0.151		
Probiotics used	3 (5.8)	6 (2.1)	2.86 (0.69, 11.81)	0.147	2.67 (0.62, 11.60)	0.189	5.93 (1.01, 34.91)	0.049*
Birth body height (cm)	49.6±1.5	49.2±1.7	1.16 (0.81, 1.66)	0.410				
Gestational Age (wk)	38.8±0.9	38.84±0.9	0.99 (0.72, 1.36)	0.960				
Birth body weigh (gm)	3,127.9±388.8	3,109.4±331.8	1.00 (1.00, 1.00)	0.721				

Values are presented as mean±standard deviation, number (%), or number only.
OR: odds ratio, CI: confidence interval, NSD: normal spontaneous delivery.
*$p<0.05$.

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DISCUSSION

The findings of this study suggest potential benefits of using 2'-FL-enriched formula in reducing the risk of IC and AD, underscoring the importance of feeding practices and targeted supplementation. Previous studies have shown that healthy infants fed 2'-FL-containing formula experience no safety concerns, with growth and tolerance profiles comparable to those fed control formula [23]. Growth and tolerance outcomes have been reported as equivalent between infants receiving experimental formulas containing 2′-FL and those receiving standard formula [24]. Interestingly, these infants exhibit cytokine concentrations similar to those of breastfed infants, suggesting an immune-modulatory role for 2'-FL [25].

HMOs, especially 2'-FL, have been associated with reduced respiratory infections and gastrointestinal inflammation, primarily by inhibiting pathogen adhesion to host epithelial surfaces [26]. In addition to this barrier function, HMOs regulate immune responses by attenuating pro-inflammatory signaling and promoting gut epithelial cell maturation [27]. These properties indicate that HMOs exert systemic effects beyond the intestinal tract and may contribute to broader aspects of infant health. Studies also suggest a role for 2'-FL in cognitive development by enhancing hippocampal plasticity and synaptic efficiency [28,29]. Furthermore, HMOs have been implicated in the prevention of necrotizing enterocolitis in preterm infants through mechanisms that improve intestinal barrier function and reduce inflammation [30]. Collectively, these findings highlight the multifactorial benefits of HMOs in supporting immune, neurological, and gastrointestinal development, benefits that may extend to the prevention of conditions such as AD and IC. However, clinical data on the relationship between HMO supplementation and these outcomes remain limited in the Taiwanese population.

AD, a prevalent allergic condition in childhood, continues to present significant public health challenges. Our findings align with previous research highlighting the rising prevalence of AD, particularly in economically developed regions such as Taiwan [8,10]. Breastfeeding has been identified as a protective factor against AD, likely through its modulatory effects on the infant gut microbiota [14]. In preclinical studies, 2'-FL has demonstrated the capacity to reduce IgE elevation and mast cell infiltration in murine models of AD [31]. The underlying mechanisms may involve enhanced production of short-chain fatty acids, which support mucosal immune function through gut microbiota regulation [32].

IC, characterized by excessive crying and irritability, is another common concern for caregivers. Our findings support prior evidence indicating a higher incidence of IC among formula-fed infants than breastfed counterparts [33]. Preventive strategies for IC emphasize maternal dietary optimization, particularly the incorporation of probiotics [34]. Probiotics may improve microbial colonization patterns, potentially reducing the incidence of IC by restoring gut homeostasis [35]. This is consistent with emerging evidence linking altered gut microbiota composition to the pathophysiology of IC. In addition, environmental, dietary, and psychosocial factors play crucial roles [34]. Creating a stable, low-stress environment and addressing maternal health conditions, such as allergic predisposition, are increasingly recognized as essential components of IC prevention [36,37]. These findings underscore the multifactorial nature of IC and support the adoption of an integrated, personalized prevention strategy.

The results from our multivariate logistic regression analysis indicated that maternal use of health supplements during pregnancy may be associated with the development of IC in

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infants, raising an important and novel question. However, this study did not collect detailed information on the specific types, dosages, or compositions of the supplements used, which may introduce confounding and limit interpretability. Given the wide range of commercially available prenatal supplements, future studies are needed to characterize supplement profiles more precisely and determine whether certain compounds may influence fetal gut or immune development in a way that predisposes to postnatal colic.

Demographic factors, such as maternal age and mode of delivery, also influence infant health outcomes [38]. Our study revealed significant differences in maternal age at delivery among the feeding groups, indicating potential confounding variables that merit further investigation. In addition, mode of delivery was significantly associated with the incidence of IC, underscoring the complex relationship between early gut microbiota colonization and infant health trajectories.

To assess growth, tolerance, and adherence related to consumption of 2'-FL-supplemented formula, our study evaluated growth metrics during the first year of life. The results demonstrated no significant differences in birth weight and head circumference across the feeding groups, consistent with prior findings showing that hydrolyzed rice formula enriched with 2'-FL was safe, well tolerated, and supported adequate weight gain in infants [39]. Additionally, a study examining the impact of brief in-hospital formula supplementation during the neonatal period [23] found no significant differences in weight gain or BMI at 12 months between these infants and their exclusively breastfed peers. These results suggest that short-term formula supplementation does not negatively impact long-term growth, reinforcing the idea that formula feeding can effectively support early development alongside breastfeeding.

Although breastfeeding remains the gold standard for infant nutrition, as recommended by the World Health Organization (WHO), infant formula remains a vital alternative. Continued advancements in the nutritional composition and safety of formula ensure that both BM and modern formula can offer health benefits, though ongoing attention to chemical safety and quality assurance remains essential [40].

Conclusions

This study highlights the multifactorial benefits of 2'-FL supplementation in infant formula. Our findings suggest that a 2'-FL-enriched formula may reduce the incidence of IC and AD, offering outcomes comparable to breastfeeding. Furthermore, infants fed 2'-FL-supplemented formula demonstrated growth metrics similar to those of breastfed infants. These insights support integrated dietary strategies to enhance infant well-being and underscore the importance of HMOs in infant nutrition.

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