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Nutrition and health value of sialic acid in early life

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ABSTRACT: Sialic acid (SA) is a naturally occurring derivative of nine-carbon monosaccharides that are typically present as oligosaccharides, glycoproteins, or glycolipids in the blood during pregnancy and in breast milk. Hepatic synthesis of SA occurs from the fetal period to 6 months after birth; therefore, exogenous SA is essential for early life growth and development. This review examines the nutritional requirements for various forms of SA in early life, considering its content in the maternal serum, breast milk, and supplementary infant foods. Additionally, it examines the synthesis and metabolism of SA, its roles in the brain and intestinal development, immune system maturation, and its efficacy in preventing and managing preterm birth and related conditions. Finally, it highlights crucial research in SA nutrition in early life to provide a scientific basis for the use of SA in infant formulas, maternal food, and medical settings.

Keywords: sialic acid; early life; nutrition; synthesis and metabolism; function; preterm birth.

1. Introduction

Sialic acid (SA), also named neuraminic acid, is a general name for a group of nine-carbon carbohydrate derivatives, of which over 50 derivatives of naturally occurring SA have been discovered. Among them, > 15 derivatives are found in humans, with N-acetylneuraminic acid (Neu5Ac) being the preponderant form in the human body, while N-glycolylneuraminic acid (Neu5Gc) is primarily found in animal milk ^[1]. SA seldom exists in free form in nature; rather, it typically exists in conjugated forms across almost all vertebrate tissues, cells, and body fluids ^[2].

Nutrition in the early 1,000 d of life is instrumental in lifelong health, and the World Health Organization (WHO) recommends breast milk from infant mothers as the preferred source of nutrition. The secretory components of breast milk contain 23.4% carbohydrates, including galactose, mannose, fucose,

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glucosamine, and SA ^[3]. Most SA (67.6–76.0%) is present in breast milk oligosaccharides, with 20.9–29.4% bound to glycoproteins, 1.6–4.8% bound to glycolipids (mainly gangliosides [GAs]), and approximately 3% present as free SA ^[4–6]. The SA content in infant formula is low; it is mainly supplemented by adding exogenous oligosaccharide-bound SA to compensate for the deficiency in base ingredients such as milk ^[7]. However, owing to regulatory and cost constraints, oligosaccharide-bound SA is not added in most infant formulas, resulting in SA primarily being present in the protein-bound form in these products ^[6, 8], which may not adequately meet infants' requirements for Neu5Ac.

The fetal brain is formed on the 28th d of pregnancy, with the explosive growth phase beginning at the 15th week after embryonic formation ^[9]. Between weeks 16 and 22, GA content in the frontal cortex is doubled, and levels in the hippocampus increase by 30%, continuing to rise for up to 4 months post-birth (Figure 1) ^[10]. In the infant brain, approximately 70% of SA is predominantly present as GAs, with breastfed infants recording brain SA levels of $487 \pm 29 \mu\text{g/g}$ at 3 months of age ^[11]. As the infant brain develops and other needs arise, serum SA levels increase during pregnancy, while breast milk SA content decreases during lactation ^[12], compensating for the limited synthesis capacity of the infant liver, thereby demonstrating the importance of exogenous SA for early life development. Therefore, changes in SA levels in the maternal serum and breast milk may affect infant health, such as preterm birth (PTB) ^[13].

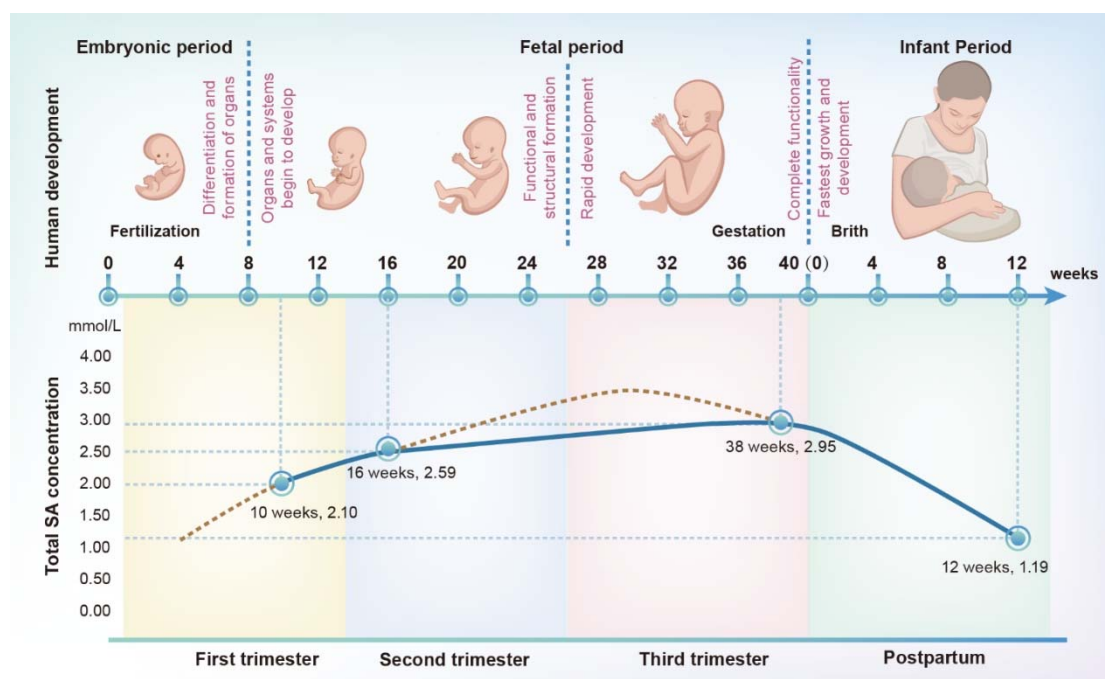


Figure 1. SA demand in early life development. SA in serum at different stages during pregnancy and lactation (based on Chhabra et al. 2015; Zhu and Li 2017). Dashed curves represent the speculated trend of changes in maternal serum SA.

Sialylation is the glycosylation process whereby SA is attached to the terminal glycans of glycoproteins and glycolipids. It is regulated by enzymes such as sialidase/neuraminidase (NEU) and sialyltransferase (ST) ^[14]. Different forms of SA perform critical biological functions by receiving antigens or other biological signals, being essential in early life brain ^[15, 16], intestinal ^[17], immune system ^[18], and bone development ^[19, 20]. Preterm infants in early life may face problems such as an insufficient SA supply, necrotizing

enterocolitis (NEC) ^[21], and late-onset sepsis (LOS) ^[22] owing to early birth. Therefore, timely SA intervention in preterm infants may have preventive and curative effects.

This review emphasizes the functional impact of SA on early life growth and development, with a focus on sialyllactoses (SLs), lactoferrin (LF), and GA. It provides the latest insights into their distinct effects in brain development, cognitive function, pathogen adhesion inhibition, and bone development. It also discusses SA's nutritional requirements, synthesis, metabolism, and application in the context of PTB.

2. Nutritional Requirements for SA in Early Life

2.1 Changes in serum SA during pregnancy

In healthy, non-pregnant women, serum SA content averages 1.19 mmol/L ^[23]. During pregnancy and up to 3 months postpartum, total serum SA content increases then decreases ^[24]. During the first trimester, serum SA levels average 2.10 mmol/L, gradually rising to approximately 2.95 mmol/L as pregnancy progresses ^[12], and returning to pre-pregnancy levels after childbirth (Figure 1) ^[24].

The serum of pregnant women contains oligosaccharide-bound SA ^[25], namely 3'-sialyllactose (3'-SL), 6'-sialyllactose (6'-SL), sialyllacto-N-tetraose a (LSTa), sialyllacto-N-tetraose b (LSTb), sialyllacto-N-tetraose c (LSTc), disialyllacto N-tetraose (DSLNT), and 3'-salivaryl lactosamine (3'-SLN). Among them, 3'-SL is the richest oligosaccharide-bound SA in the serum of pregnant women and is associated with low-density lipoprotein levels and elevated total cholesterol in the third trimester ^[26]. Total serum GA content also increases as pregnancy progresses, with 89–94% comprising monosialoganglioside 3 (GM3), followed by disialoganglioside 3 (GD3). However, serum content of GM2, GD1a, and GD1b decrease from the second to the third trimester, and total serum GA content decreases in some pregnant women ^[27]. Notably, the serum content of LF, the major protein-bound SA, does not change significantly during pregnancy ^[28].

The increase in serum SA during pregnancy is largely due to increased maternal synthesis in the third trimester. This SA can cross the placenta, helping protect the fetus from inflammatory mediators and supporting fetal growth and development ^[29–31]. Brain development, in particular, requires a sufficient maternal SA supply, as rapid brain growth begins in the second trimester, peaking at around 30 weeks of gestation ^[32]. GA concentrations remain high in the cortex until this period ^[10], suggesting that maternal serum SA peaks at approximately 30 weeks of pregnancy (Figure 1). Additionally, elevated SA content may be influenced by pregnancy-associated estrogen secretion ^[12]. For instance, α 2,3SA and α 2,6SA contents in amniotic fluid are higher during the third trimester than during the second trimester and significantly decrease in post-term pregnancies. Similarly, maternal estriol content peaks during the third trimester before declining during delivery, showing a pattern that follows the changes in amniotic fluid and maternal serum SA contents ^[33].

Serum total SA (TSA) content is higher in preterm pregnant women than that in healthy pregnant women ^[12]. This increase may stem from the secretion or shedding of free SA from cell surfaces or membranes, release of cellular lipid-bound and protein-bound SA, and increased production of SA-rich

inflammation-sensitive proteins [13]. Therefore, pregnant women with preeclampsia, characterized by hypertension and proteinuria in the second half of pregnancy, show significantly increased levels of both protein-bound and free serum SA, likely due to increased production of serum glycoproteins and enhanced NEU activity [34]. SA-binding immunoglobulin-like lectins (Siglecs) are a type of protein-bound SA expressed in many cell types of the immune system [35]. Pregnant women with preeclampsia exhibit increased Siglec-6 expression in the placenta, which can be regarded as a prospective biomarker and target for clinical diagnosis and treatment [36].

2.2 Changes in SA patterns in breast milk

Breast milk is abundant in various forms of SA found in oligosaccharides, glycoproteins, and glycolipids, with a small fraction existing in a free form (Figure 2) [6]. Among them, oligosaccharide-bound SA is predominantly composed of 3'-SL and 6'-SL [37]. Lipid-bound SA is primarily composed of GM3 and GD3 [38]. Protein-bound SA is primarily composed of LF [39]. The predominant form of free SA is Neu5Ac [6]. Notably, breast milk SA content varies based on molecular composition, lactation stage [5, 6], gestational age [4, 40], maternal diet [41, 42], and regional factors [43].

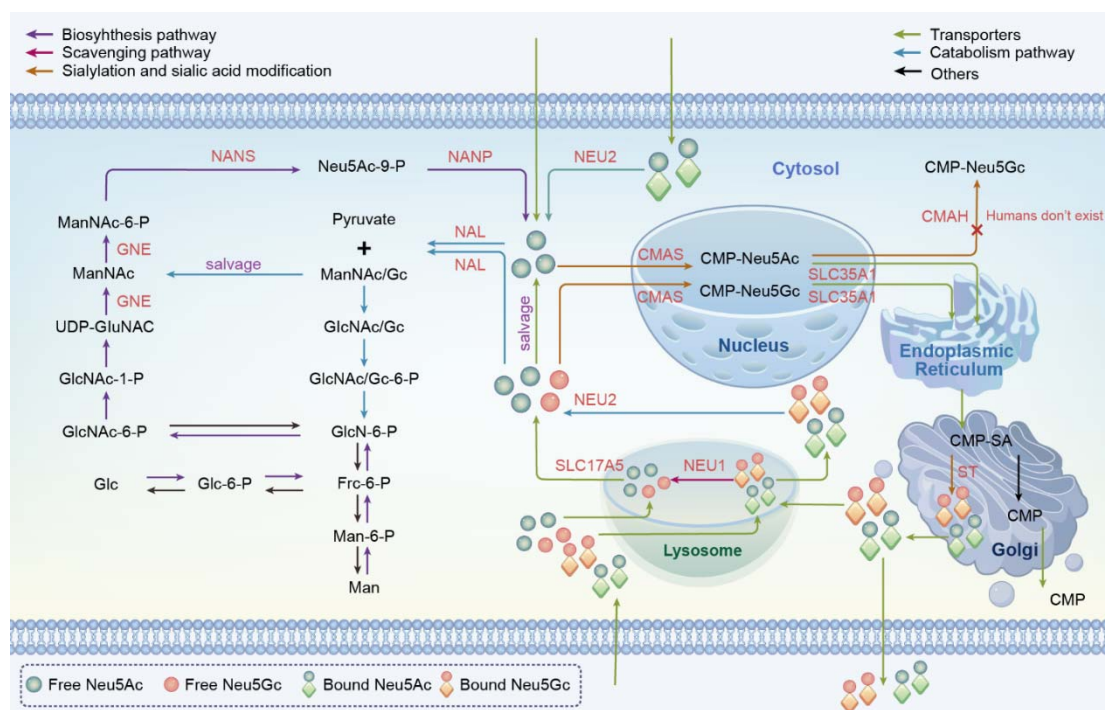


Figure 2. Diagram of the SA metabolism process in mammalian cells. Glc, glucose; Glc-6-P, glucose-6 phosphate; Fru-6-P, fructose-6-phosphate; GlcN-6-P, glucosamine-6- phosphate; GlcNAc, N acetylglucosamine; GlcNGc, N-glycolylglucosamine; GlcNAc-6-P, N-acetylglucosamine-6-phosphate; GlcNGc 6-P, N-glycolylglucosamine-6-phosphate; GlcNAc-1-P, N-acetylglucosamine-1-phosphate; UDP-GlcNAc, uridine 5'-diphosphate-N-acetylglucosamine; Man, mannosamine; Man-6-P, mannosamine-6-phosphate; ManNAc, N-acetylmannosamine; ManNGc, N-glycolylmannosamine; ManNAc-6-P, N-acetylmannosamine-6 phosphate; ManNAc-9-P, N-acetylmannosamine-9-phosphate; Neu5Ac, N-acetylneuraminic acid; CMP Neu5Ac, cytidine 5'-monophospho-N-acetylneuraminic acid; CMP-Neu5Gc, cytidine 5'-monophospho-N glycolylneuraminic acid; Neu5Gc, N-glycolylneuraminic acid; CMP, cytidine 5'-monophosphate; CMP-SA, cytidine 5'-monophospho-sialic acid; GNE, uridine 5'-diphosphate-N-acetylglucosamine 2-epimerase/N acetylmannosamine kinase; NAL, sialic acid aldolase/N-acetylneuraminic pyruvate-lyase; NANS, sialic acid synthase; NANP, N-acylneuraminic 9-phosphatase; NEU1, neuraminidase 1; NEU2, neuraminidase 2; CMAS, cytidine 5'-monophosphate N-acetylneuraminic acid synthetase; ST, sialyltransferase; CMAH, cytidine 5' monophosphate-N-acetylneuraminic acid hydroxylase.

2.2.1 Lactation stage

Colostrum, produced during the first 0–7 d postpartum, is rich in SA but consumed in small amounts, aiding newborns with underdeveloped digestive systems. Owing to immature liver function, infants rely on exogenous SA for early development [8]. With prolonged lactation, the infants' liver function gradually improves, their ability to synthesize SA is enhanced, and the amount of SA in breast milk gradually decreases [40]. The downward trend of oligosaccharide-bound SA is more pronounced than that of free and protein-bound SA [4, 40].

Various oligosaccharide-bound SA forms, including 3'-SL, 6'-SL, LSTa, LSTb, LSTc, DSLNT, 3'-sialyl-3-fucosyllactose, and 6'-sialyllactosamine (6'-SLN), have been found in breast milk [37]. Among these, the content of 6'-SL is the highest in colostrum and decreases throughout lactation, whereas the level of 3'-SL is relatively stable throughout lactation [44]. However, over a longer period (0–400 d postpartum) [45, 46], 6'-SL levels increase from colostrum to transitional milk (8–15 d) before significantly decreasing in mature milk (after 16 d). In contrast, 3'-SL shows a U-shaped pattern, first decreasing then increasing. In addition, the LSTb and DSLNT contents in the sialylated human milk oligosaccharides (HMOs) do not change over time [47].

Several types of GAs are present in breast milk, including monosialogangliosides and disialogangliosides, with GM3 and GD3 being the primary species. GM3 predominates in mature milk, while GD3 is the predominant glycolipid in colostrum [27, 48]. Total GAs exhibit a U-shaped pattern from 0 to 400 d postpartum, positively correlating with total phospholipid concentrations. During this time, GM3 content steadily increases, while GD3 content decreases, likely influenced by the lipid content in breast milk [49].

Key protein-bound SA components in breast milk include LF, secretory immunoglobulins A (sIgA), and κ -casein. LF content is highest in colostrum but decreases during the first month, stabilizing thereafter [50, 51]. κ -casein, the only sialylated casein in breast milk, has an oligosaccharide moiety rich in SA. Its content increases from colostrum to transitional milk but gradually declines after the third month [52]. sIgA, which constitutes 80–90% of breast milk immunoglobulins, decreases sharply during the first week postpartum and remains stable thereafter [53]. Moreover, osteopontin (OPN) levels are highest and most stable in colostrum but decline throughout the first year of lactation [54].

2.2.2 Gestational age

SA content is higher in preterm breast milk than in term breast milk, although the types of SA are essentially the same. However, the decline in SA content over time is more pronounced in preterm breast milk than in term breast milk. By 3 months of lactation, the differences in oligosaccharide-bound and free SA content between preterm and term breast milk become no longer significant [4, 40].

The levels of sialylated HMOs such as 3'-SL, LSTb, and DSLNT are high in preterm breast milk during the first 2–8 weeks postpartum, whereas those of LSTc (at weeks 1–4) and 6'-SL (at weeks 2–4) are high in term breast milk during the first month postpartum. This variation may be due to differences in ST activity.

After PTB, the ST responsible for linking SA to galactose via the α -1,6 bond shows reduced activity, whereas the ST responsible for α -1,3 linkages to galactose or α -1,6 linkages to N-acetylglucosamine exhibits increased activity [55].

Total lipid-bound SA content peaks 2–3 d postpartum and remains elevated for approximately 10 d. GD3 content in preterm colostrum is comparable to term colostrum, whereas GM3 content is lower and increases slowly over time. However, the total GM3 content in preterm breast milk is lower than that in term breast milk, with a slow rate of increase over time [38].

Protein-bound SA content is significantly higher in preterm breast milk than in term breast milk, except in colostrum [4]. In colostrum, sIgA and OPN levels are significantly upgraded [53, 56], potentially enhancing its antimicrobial activity during the early postnatal period. Geographic and ethnic factors influence LF levels, which remain significantly high from colostrum to mature milk of preterm mothers [50], reflecting the increased demand for LF in preterm infants. However, variations in LF and OPN contents in preterm milk reported in previous studies are likely because of small sample sizes, inconsistent detection methods, and differences in study design, making definitive conclusions difficult.

2.2.3 Maternal diet and regional factors

Lactating mothers supplemented with vitamin A show significantly high levels of both free and conjugated SA, possibly because of increased Neu5Ac synthesis or the presence of both nutrients in the same food source [41]. Sialylated HMOs are weakly and positively correlated with maternal dietary vitamin A, β -carotene, and α -tocopherol levels during lactation. Additionally, vitamin B2 is positively correlated with elevated 3'-SL content [57]. Despite this, the SA content in breast milk, especially transitional breast milk, is considerably higher than typical dietary intake levels (95–128 mg/d), suggesting that breast milk SA is more likely derived from maternal synthesis or body reserves, and, thus, may have only a limited correlation with dietary SA intake [5].

Sialylated glycans are 1.8 times more abundant in the Han Chinese population than in the Hui and Tibetans. This difference is linked to dietary patterns; for example, Han individuals primarily consume wheat-based carbohydrates, various vegetables, and limited meat, while the Hui and Tibetans consume more beef and lamb but few vegetables [58]. The dietary intake of vegetables and vitamins positively correlates with HMOs content [42]. Notably, a high-fat diet results in a lower content of sialylated HMOs than that from a high-carbohydrate diet [57]. LF content in the milk of Chinese Dai and Han mothers is significantly higher than that of Tibetan mothers. Similarly, mothers from Guangdong in southern China have higher LF levels in their milk than in the maternal milk of mothers from northern provinces such as Heilongjiang and Gansu [50]. In Spain, breast milk SA content is significantly lower in the central region than in the coastal areas [59]. LSTb and LSTc contents are more abundant in breast milk from mothers in Australia than in other countries [43]. Table 1 summarizes regional differences in breast milk SA content in across China and other countries at various time points. However, comparing SA changes within and between regions remains challenging owing to factors such as differences in sampling and sample analysis, and limited sample sizes.

Table 1. Content of SA in breast milk across different regions and stages

Country	City	Gestational age	Unit	Type	0–7 d	7–15 d	30–45 d	90–100 d	> 100 d
China	Weifang ^[12]	Term	mmol/L	TSA	5.15 ± 0.18	-	1.99 ± 0.08	0.53 ± 0.04	-
	Hangzhou ^[60]	PTB	mg/L	TSA	2,302.6 ± 609.0	1,556.3 ± 420.4	-	424.7 ± 95.1	317.4 ± 82.9
					2,161.0 ± 695.5	-	1,361.7 ± 413.7	376.6 ± 92.4	262.1 ± 72.1
	Beijing ^[40]	PTB	mg/L	TSA	1,338.06 ± 363.05	1,117.21 ± 146.56	808.09 ± 193.76	-	247.11 ± 74.48
					1,132.84 ± 268.24	1,016.85 ± 228.32	607.46 ± 238.10	-	233.81 ± 59.99
		Term	mg/L	TSA	1,670.74 ± 94.53	1,272.19 ± 128.74	541.64 ± 55.20	297.65 ± 20.78	-
					1,210.71 ± 68.13	917.28 ± 92.40	395.71 ± 40.75	213.57 ± 15.23	-
	Xiamen ^[5]	Term	mg/L	PBSA	408.45 ± 25.16	316.82 ± 33.28	129.41 ± 12.89	74.82 ± 5.13	-
					51.58 ± 2.92	38.08 ± 3.85	16.52 ± 1.78	9.26 ± 0.60	-
				FSA	1,160 ± 200 ^a	500 ± 20 ^a	250 ± 10 ^a	-	50 ± 5 ^a
					891.48	360 ± 30 ^a	150 ± 20 ^a	-	22.12
	Nanchang ^[6]	Term	mg/L	PBSA	220.81	100 ± 10 ^a	70 ± 10 ^a	-	27.32
				LBSA	18.88	12 ± 1 ^a	7.5 ± 0.5 ^a	-	3.01
				FSA	33 ± 5	12 ± 1 ^a	17 ± 3 ^a	-	9 ± 2 ^a
				OBSA	1,138 ± 86	706 ± 79	348 ± 63	135 ± 16	-
America	Oxford ^[61]	-	mg/L	PBSA	267 ± 24	192 ± 33	133 ± 27	73 ± 8	-
Italy	Ancona ^[62]	Term	g/L	OBSA	3.30	2.70	2.14	1.58	-
Japan	[63]	Term	mg/L	OBSA	1,131.7	923.9	598.8	295.8	-
		PTB	mg/L	LBSA	60.0 ± 13.5	35.6 ± 9.3	27.8	54.6	-
Spanish	[64]	Term	mg/L	OBSA	1,018 ± 229	696 ± 245	365 ± 133	-	-
	Madrid ^[59]	Term	mg/100 mL	TSA	101.6 ± 7.6	89.4 ± 4.5	51.0 ± 1.6	26.6 ± 0.9	24.5 ± 2.1
	Murcia ^[59]	Term	mg/100 mL	TSA	136.1 ± 8.4	92.3 ± 1.5	61.0 ± 4.1	33.7 ± 0.7	30.2 ± 0.9
	Valencia ^[59]	Term	mg/100 mL	TSA	136.1 ± 8.4	92.3 ± 1.5	52.5 ± 2.2	36.1 ± 2.2	31.9 ± 2.5
	[52]	Term	mg/L	TSA	1,277.0 ± 261.9	910.8 ± 275.6	525.8 ± 170.4	-	-
					1,063.7 ± 238.9	720.6 ± 254.1	411.2 ± 163.0	-	-
				PBSA	149.1 ± 43.1	108.2 ± 27.8	72.8 ± 34.2	-	-
				LBSA	2.42	1.43	0.83	-	-
Australia	Sydney ^[4]	PTB	mmol/L	FSA	34.7 ± 3.7	22.1 ± 2.4	16.2 ± 1.4	-	-
				TSA	5.76 ± 0.19	4.27 ± 0.24	2.56 ± 0.15	1.30 ± 0.13	-
				OBSA	3.72 ± 0.15	2.64 ± 0.14	1.48 ± 0.07	0.73 ± 0.05	-
				PBSA	1.18 ± 0.09	0.73 ± 0.03	0.43 ± 0.03	0.29 ± 0.02	-
		Term	mmol/L	FSA	0.14 ± 0.01	0.09 ± 0.01	0.07 ± 0.003	0.03 ± 0.001	-
				TSA	5.04 ± 0.21	3.46 ± 0.14	1.98 ± 0.08	1.04 ± 0.06	-
				OBSA	4.27 ± 0.15	3.16 ± 0.18	1.89 ± 0.11	0.91 ± 0.12	-
				PBSA	1.30 ± 0.08	1.01 ± 0.08	0.58 ± 0.05	0.37 ± 0.04	-
				FSA	0.19 ± 0.02	0.11 ± 0.02	0.10 ± 0.01	0.03 ± 0.01	-

Note: Data marked "a" are an estimate based on the given graph; they do not directly appear in the original text. Mark "-", not detected or no available data.

Abbreviations: OBSA, oligosaccharide-bound sialic acid; PBSA, protein-bound sialic acid; LBSA, lipid-bound sialic acid; FSA, free sialic acid; TSA, total sialic acid; PTB, preterm birth.

2.3 SA content in infant supplementary food

The WHO recommends exclusive breastfeeding for the first 6 months of life, followed by the gradual introduction of complementary foods for up to 2 years when possible ^[65], allowing infants to obtain free and conjugated SA from foods such as powdered milk, cow's milk, and eggs. Some natural resources contain high levels of SA, primarily in the form of bound SA, including edible bird's nests (EBNs), crucian carp eggs, caviar, and milk (Table 2).

Neu5Gc is primarily obtained through dietary intake, while Neu5Ac is the predominant SA form found in infant foods. In animals, Neu5Gc levels are typically higher in the brain and viscera than in muscle, with the brain containing the most conjugated Neu5Gc and TSA content, while the liver has the highest free Neu5Gc content. The conjugated form of Neu5Gc is more abundant than the free form across all organs ^[66]. Even though fish possess the *cytidine 5'-monophosphate N-acetylneuraminic acid hydroxylase (CMAH)* gene, most species have little to no Neu5Gc. However, caviar has an unusually high Neu5Gc content at 445–530 µg/g ^[67]. Common plant-based foods such as fruits, vegetables, and grains do not contain SA, likely because they lack the pathway for SA synthesis ^[67, 68]. However, lower levels of Neu5Ac have been found in mung bean sprouts and apples, possibly because of foreign pollutants introduced during the detection process ^[69]. High levels of both Neu5Ac and Neu5Gc are found in cooked corn ^[30], along with B-carotene, an adequate source of vitamin A. Foods rich in vitamin A, such as red meat, cow's milk, and eggs, are associated with high SA levels ^[42]. This relationship highlights the overlap between SA and vitamin A in dietary sources, which likely contributes to the high SA content observed in breast milk.

Unlike breast milk, where oligosaccharide-bound SA is most abundant, supplementary infant foods primarily contain protein-bound SA ^[6, 8]. The contents of free SA in sheep, cow, and goat milk are only marginally inferior to that in breast milk ^[6]. The mean consumption of total GAs in Malaysian infants aged 1–2 years is 5.86 ± 0.56 mg/d, whereas that in Chinese infants is 4.21 mg/d ^[48]. Currently, animal-based foods and dairy products are recognized as the primary contributors to SA content in complementary foods. More studies are also needed to determine the exact amount of SA that infants obtain from different dietary sources.

Table 2. SA content of common supplementary foods for infants

Food category	Biological material	Unit	Neu5Ac	Neu5Gc	TSA
Eggs and their derivatives ^[7, 67]	Crucian eggs	µg/g	4,574.3	0	4,574.3
	Egg yolk	µg/g	1,110.3	0	1,110.3
	Egg white	µg/g	367.6	0	367.6
	Caviar	µg/g	-	445–530	1,534–4,077
Milk and dairy products ^[6, 7, 70]	Cheese	µg/g	204.9	6.7	289.0
	Milk	µg/g	197.5	10.9	237.4
	Sheep milk	µg/mL	46.26	15.69	61.95
	Goat milk	µg/mL	67.44–89.72	19.69–100.01	87.13–189.73
	Bovine milk	µg/mL	47.02–155.64	0–3.84	49.53–159.58
	Dry formula	mg/g	28.21–250.55	2.07–153	44.4–257.22
Meat ^[7]	Yogurt	µg/g	158.9	6.9	222.0

Food category	Biological material	Unit	Neu5Ac	Neu5Gc	TSA
Bird's nest ^[71] Aquatic products ^[67]	Beef	μg/g	46.2	30.3	76.7
	Pork	μg/g	57.1	5.6	62.6
	Duck	μg/g	67.2	0	67.7
	Chicken	μg/g	56.7	0	57.0
	Lame	μg/g	70.0	20.4	90.6
	Edible bird's nest	μg/g	95,100.0	0	95,100.0
	Crucian carp	μg/g	53.6	1.5	55.2
	Grass carp	μg/g	45.2	0.5	45.6
	Golden pomfret	μg/g	74.9	0	74.9
	Prawn	μg/g	7.9	1.1	9
Vegetables and fruits ^[68, 69]	Shellfish	μg/g	-	0	-
	Tomato	μg/g	0	0	0
	Spinach	μg/g	0	0	0
	Banana	pmol/g	0	-	-
	Apple	pmol/g	6.7	-	-
Cereals ^[30, 68]	Mung bean sprout	pmol/g	2.7 ± 1.8	-	-
	Potato	μg/g	0	0	0
	Corn(cooked)	μg/g	39.1	21.7	61

Mark "-", not detected or no available data.

3. SA Metabolism in Infants

3.1 SA anabolism

As the infant's organs mature, the infant synthesizes SA using glucose or other glycolytic products as a raw material, mainly through a four-step process involving three critical enzymes in the cytosol (Figure 2) ^[72]. Uridine 5'-diphosphate-*N*-acetylglucosamine (UDP-GlcNAc), 2-epimerase/*N*-acetylmannosamine (ManNAc) kinase (GNE), SA synthase (NANS), and cytidine 5'-monophospho (CMP) *N*-acetylneuraminate acid synthetase (CMAS) are required for SA synthesis, whereas dephosphorylation by *N*-acylneuraminic 9-phosphatase (NANP) appears nonessential ^[73].

Among these, GNE has the highest expression in the placenta and liver ^[74, 75]. Notably, complete knockout of the mouse *Gne* gene leads to complete absence of endogenous SA production, ultimately causing early embryonic lethality ^[76]. The activity of hepatic SA synthesis in rats gradually increases during the first 9 d after birth. After weaning, the expression of GNE and NANS in the colon becomes higher than during lactation ^[75]. This pattern suggests that SA synthesis in the liver of rat pups increases in parallel with milk intake; when SA levels in breast milk are low, endogenous SA synthesis in the colon may be activated.

The epimerase function of GNE transforms UDP-GlcNAc into ManNAc by removing the UDP moiety and epimerizing GlcNAc. Subsequently, GNE's kinase function phosphorylates ManNAc to produce ManNAc-6-P ^[72]. NANS facilitates the condensation reaction between ManNAc-6-P and phosphoenolpyruvate to form Neu5Ac-9-P, which is subsequently dephosphorylated by NANP to generate Neu5Ac ^[73]. If the *NANS* gene has a mutation, it will block the endogenous synthesis of Neu5Ac and lead to the accumulation of the precursor ManNAc-6-P ^[77]. All aforementioned processes occur in the cytoplasm.

Consequently, Neu5Ac can be catalyzed by CMAS and activated in the nucleus to be converted into CMP-Neu5Ac ^[78]. It is transported by Slc35A1 to the endoplasmic reticulum and enters the Golgi apparatus ^[79], where ST uses CMP-activated SA to sialylate the terminal galactose residues of the oligosaccharide

chains of free oligosaccharides or glycoconjugates. This process leads to the synthesis of glycoprotein and GA, which are ultimately secreted or transported to the cell surface to fulfill their biological functions [80].

While Neu5Gc is present in almost all mammals, only small quantities are found in healthy human tissues and on the surface of human tumor cells. This is because of the incorporation of Neu5Gc into glycoproteins and glycolipids primarily from dietary intake (e.g., red meat and milk) [81]. CMP-Neu5Ac can be converted to CMP-Neu5Gc by CMAH in the cytosol, which is then transported to the Golgi apparatus for further processing [79]. However, because inactivation mutations in the *CMAH* gene are mediated by Alu, humans cannot convert Neu5Ac to Neu5Gc [82]. In a *Cmah*-knockout mouse model, dietary supplementation with Neu5Gc increased Neu5Gc levels in tissues [83]. Similarly, mammalian cells supplemented with exogenous Neu5Gc exhibited elevated Neu5Gc content [79]. Thus, infants rely primarily on dietary sources for Neu5Gc, consuming Neu5Gc-rich foods in daily life.

3.2 Digestion and absorption

Based on animal studies, neonates lack full capacity to synthesize SA at birth, and the high levels of SA in breast milk during lactation compensates for the limited ability of the neonatal liver to produce endogenous SA [75]. The SA transporter protein SLC17A5 is essential in SA metabolism [84]. Pathogenic variants in the *Slc17A5* gene result in the accumulation of free SA in lysosomes. Studies in mice with *Slc17A5* knockout have shown significant free SA accumulation (66 nmol/mg protein), delayed neurodevelopment, stunted growth, and a severely shortened lifespan [85].

The metabolic pathways of exogenous (dietary) SA is related to the form wherein it is present (Figure 2) [30]. Healthy infants cannot fully digest conjugated Neu5Ac because the digestive system is immature, and oligosaccharides and proteins are highly resistant to hydrolysis in the gut. Most Neu5Ac and unhydrolyzed conjugated Neu5Ac are transported through the bloodstream and excreted in urine and feces, while the remaining portion of released Neu5Ac enters the cytoplasmic lysosome [86]. Conjugated Neu5Ac undergoes hydrolysis by NEU to produce Neu5Ac, amino acids, fatty acids, and other metabolites, whereas free SA can also be released via NEU activity [30]. NEUs are distributed in various cellular locations, including lysosomes (NEU1), the cytosol (NEU2), the outer plasma membrane (NEU3), and intracellular membranes (NEU4) [72, 80]. A small amount of dietary SA is transferred from the extracellular space into lysosomes via receptor-mediated endocytosis, hydrolyzed by NEU1 to form Neu5Ac, and transported to the cytosol through SLC17A5 for CMP-SA synthesis [87]. SA aldolase/N-acetylneuraminate pyruvate-lyase is a key enzyme in SA catabolism, cleaving Neu5Ac into pyruvate and ManNAc [72]. ManNAc can be recycled via ManNAc kinase or metabolized further by GNE to GlcNAc. Then, GlcNAc is phosphorylated by GlcNAc kinase to improve GlcNAc-6-phosphate formation, which is converted into glucosamine 6-phosphate and proceeds to enter the hexosamine biosynthetic pathway [80]. Cytoplasmic Neu5Ac can also be activated by coupling it with CMP, after which it is transported to the Golgi apparatus to participate in the synthesis of SA glycoconjugates [75].

Dietary conjugated Neu5Gc is similarly metabolized to conjugated Neu5Ac, arriving at the lysosome via clathrin- and caveolin-dependent endocytosis pathways [30, 79]. Free Neu5Gc is subsequently released from the glycoconjugate via lysosomal NEU1, exported in free form into cytoplasmic lysosomes, and translocated to the nucleus via CMP. Subsequently, Neu5Gc is activated by CMAS to form CMP-Neu5Gc, which is translocated to the Golgi apparatus to participate in the synthesis of sialylated glycoconjugates [79, 88].

The bioavailability of different SA forms can also vary. The knockout of the *Cmah* gene in mice has been used to study the metabolic mechanisms of free Neu5Gc and Neu5Gc-glycoproteins. Free Neu5Gc ingested from the diet disappears rapidly from the intestine, with peak blood levels occurring within 1 h. It is then excreted in the urine within 1–2 h. Neu5Gc-glycoproteins are ingested by the small intestine and subsequently transported through the body in the form of glycoconjugates [89]. In contrast, dietary Neu5Gc from red meat is readily absorbed by the body and can be integrated into the brain or other organs. However, dietary free Neu5Ac is immediately excreted through urine after intestinal absorption and does not undergo utilization by the human body [1]. The use of ^{19}F to label SA to track its biodistribution and metabolism has revealed that the brain absorbs less SA than the kidneys, and the uptake of SA by the brain and kidneys gradually decreases with age [90]. Moreover, after 7 d of oral administration of EBN to mice, the content of TSA (Neu5Gc + Neu5Ac + deaminoneuraminic acid) increases in the serum, spleen, and lung tissues, with Neu5Ac being the predominant form of SA in brain tissues, whereas Neu5Gc is the main form found in serum and other tissues [91]. Notably, SA metabolism varies by species, age, and SA form, thus, findings from animal or cell studies may not accurately reflect glycosylation processes in infants. The potential long-term effects of increased Neu5Gc intake on neonatal or infant development remain unclear.

4. SA Function on Growth and Development in Early Life

A large body of in vitro and in vivo evidence demonstrates that SA is crucial in early development, including enhancing brain development and cognition, improving gut maturation, and supporting bone growth (Figure 3). The beneficial function of SA on infants is presented in Table 3.

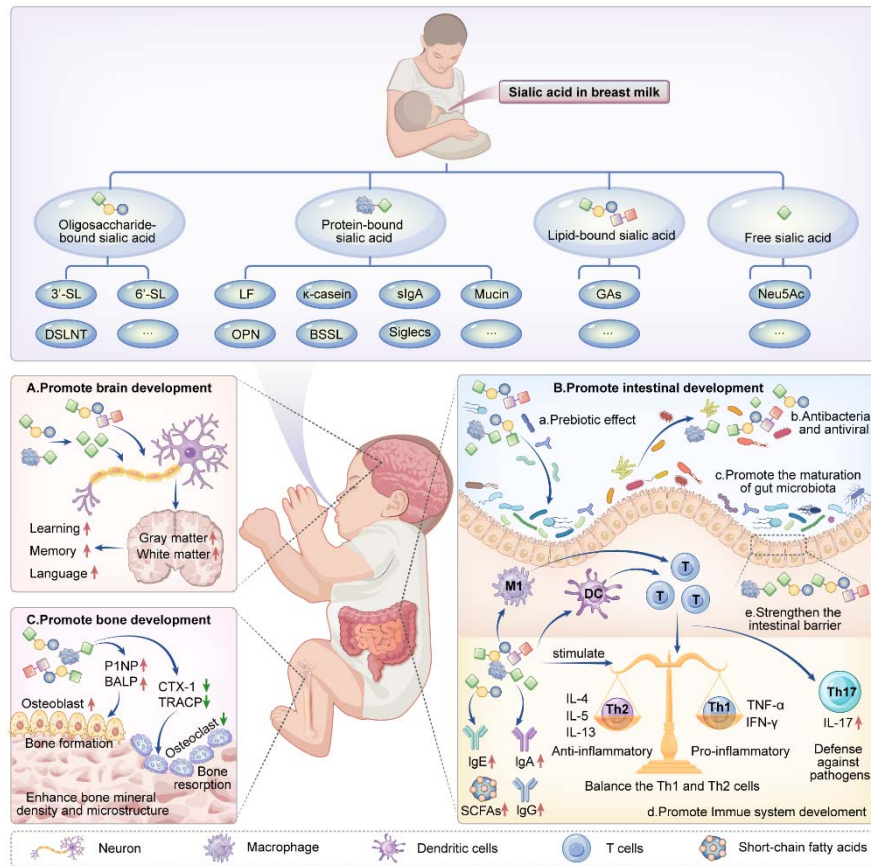


Figure 3. Biological functions of different forms of SA in infants. **A** Lipid-bound SA directly acts on the brain. Protein-bound and oligosaccharide-bound SA are released into free forms before upregulating NGF and BDNF, thereby promoting brain development. **B** As a prebiotic, SA promotes the growth of probiotics such as bifidobacteria, further inhibiting the colonization of pathogenic bacteria. Acting as bait receptors, SA molecules directly interact with pathogens to prevent their invasion. SA also protects intestinal mucus integrity, alleviates inflammation of intestinal epithelial cells, and enhances epithelial barrier function. By optimizing gut microbiota composition and increasing the production of short-chain fatty acids and plasma IgA, IgE, and IgG, as well as activating dendritic cells and M1 macrophages, SA helps achieve balanced T-cell responses and contributes to immune system maturation. **C** SA promotes osteoblast proliferation and differentiation, inhibits osteoblast apoptosis, and suppresses osteoclast development. SA, sialic acid; SL, sialyllactose; DSLNT, disialyllacto-N-tetraose; LF, lactoferrin; OPN, osteopontin; BSSL, bile salt-stimulated lipase; sIgA, secretory immunoglobulin A; Siglecs, SA-binding immunoglobulin-like lectins; GAs, gangliosides; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; IL, interleukin; Ig, immunoglobulin; Th1, T helper type 1 cell; Th2, T helper type 2 cell; Th17, T helper type 17 cell; TNF- α , tumor necrosis factor-alpha; IFN- γ , interferon-gamma; P1NP, pro-collagen type 1 N-terminal propeptide; BALP, bone alkaline phosphatase; CTX-1, C-telopeptide of type I collagen; TRACP, tartrate-resistant acid phosphatase.

4.1 Oligosaccharide-bound SA function

Rats and mice have been generally used for studying the function of SA, and oligosaccharides in their milk mainly bind to SA in the form of 3'-SL and 6'-SL, similar to the characteristics of human milk [92]. Oligosaccharide-bound SA deficiency in the early stages of life leads to impaired cognitive functions in memory and attention [93]. In previous studies, mouse models lacking the *St6gal1* or *St3gal4* genes for sialylated lactose synthesis were established using a gene knockout method. The results revealed that the absence of sialylated lactose negatively impacted neurodevelopment [94-96].

SA, present in oligosaccharide-bound forms, is crucial for the synthesis of GAs and myelin sheath, serving as a critical component of cortical gray and white matter, highlighting its essential role in brain

development^[97]. In preterm pigs supplemented with SLs, genes associated with SA metabolism, myelin formation, and GA biosynthesis are upregulated^[98]. Additionally, in human infants, breast milk 3'-SL concentrations are positively correlated with enhanced fractional anisotropy, reduced mean diffusivity, and increased regional cerebral blood flow in developing white matter at 1-month-old^[97]. Furthermore, SLs correlate positively with improvements in language development and motor skills in children aged 2–25 months, suggesting that SLs may enhance learning, memory, and language functions^[15, 16].

Wang and Rui^[96] stated that 6'-SL knockout in the milk of lactating rats resulted in low gut microbiota diversity in offspring rats. Sialylated HMOs, particularly 6'-SL, significantly affected the infant gut microbiota, enhancing the growth of bifidobacteria in the infant's intestine^[99]. Combined supplementation with 6'-SL and 3'-SL stimulates intestinal maturation and prevents diarrhea by upregulating the expression of glial cell line-derived neurotrophic factor. This enhances phosphorylation of cAMP response element-binding protein and improves synthesis of polysialic acid (PSA)^[100]. Furthermore, SLs enhance mucosal and immune responses by stimulating dendritic cell (DC)- and M1 macrophage-mediated Th1 (interferon [IFN]- γ) and Th17 (interleukin [IL]-17) responses, while inhibiting Th2 (IL-13) responses^[101].

In a mouse model of dermatitis, 3'-SL treatment weakened T cell differentiation and reduced Th1 cytokine (tumor necrosis factor alpha [TNF- α] and IFN- γ), Th2 cytokine (IL-4, IL-5, and IL-13), and immunoglobulin E (IgE) production^[102]. When combined with 2'-fucosyllactose (2'-FL), 6'-SL also mitigates lipopolysaccharide (LPS)-induced inflammation by increasing the production of short-chain fatty acids (SCFAs)^[103]. Notably, a 2'-FL:6'-SL ratio of 5:1, closely resembling that found in breast milk, has been confirmed to be most effective in alleviating inflammation. Oligosaccharide-bound SA binds to intestinal epithelial cells, significantly reducing the adhesion of enteropathogenic *Escherichia coli*^[104].

Since the structure of HMOs is homologous to glycans on the surface of epithelial cells, which inhibit cell attachment as soluble bait receptors for pathogens, 3'-SL exerts a potent inhibitory effect on H1N1 viral cells. Additionally, 3'-SL (200 $\mu\text{g/mL}$) binding to OPN (500 $\mu\text{g/mL}$) significantly reduces the levels of TNF- α , IL-6, and iNOS, thereby enhancing innate immunity^[105]. Rotavirus (RV) is the primary factor responsible for acute gastroenteritis in infants. Notably, supplementation with both 6'-SL and 3'-SL reduces the infectivity of the RV G2P strain by 73%, higher than that of the individual treatments of 6'-SL (40%) or 3'-SL (47%)^[106].

The bones rely on the coordinated activity of two major types of cells during growth and metabolism^[107]: osteoclasts, which resorb old bone, and osteoblasts, which form new bone. Notably, 3'-SL promotes osteogenic differentiation via the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, while inhibiting adipogenic differentiation. Additionally, it suppresses osteoclast differentiation through the nuclear factor kappa B (NF- κB)/mitogen-activated protein kinase (MAPK) signaling pathway, thereby maintaining bone homeostasis and reducing bone loss^[19, 108].

4.2 Protein-bound SA function

Piglets are very similar to newborns in terms of brain structure, function, and digestive system, making them ideal for use as model organisms ^[109]. Dietary intervention with low concentrations of LF (155 mg/kg/d) improved neurodevelopment and cognition through upregulation of the brain-derived neurotrophic factor (BDNF) signaling pathway in piglets, whereas high concentrations (285 mg/kg/d) were neuroprotective through LF receptors ^[39, 110]. OPN supplementation results in enhanced brain development in mouse pups by upregulating the expression of proteins associated with brain myelin formation, including myelin-associated glycoprotein and myelin basic protein ^[111]. Similarly, casein glycomacropeptide (CGMP) supplementation upregulates the learning-associated genes *GNE* and *ST8SIA4* during early development, promoting piglet brain growth ^[112].

A randomized clinical trial demonstrated that feeding healthy full-term infants at 2 weeks of age with formulas administered with bovine LF (bLF; 0.6 g/L) and milk fat globule membrane accelerated neurodevelopmental status by day 365 and improved language development and diarrhea outcomes by day 545 ^[113]. Moreover, weaning and the addition of 76 mg/100 g bLF formula for 3 months in 108 anemic infants aged 6–9 months is the most beneficial in reducing respiratory infections incidence and diarrhea among infants with anemia ^[114]. RV is a major pathogen associated with severe diarrheal disease in infants and children. Neutralization of RV by LF (≥ 8 mg/mL) results in decreased expression of toll-like receptor (TLR)-7 in Caco-2/TC7 cells, with bLF being the most effective form ^[115].

During lactation, LF-lacking mice offspring exhibits reduced intestinal barrier function and weakened innate immunity that persist into adulthood, possibly due to decreased actin expression and secretion of α -defensins in the small intestine ^[116, 117]. In a piglet model, recombinant formula milk rich in human LF (hLF) improved systemic and intestinal immune responses by upregulating Th cytokines production, enhancing B cell activity, and increasing plasma IgG and IgA secretion ^[118]. hLF also reduces pro-inflammatory responses by downregulating TNF- α and IL-6, attenuating immune responses via the TLR pathway in neonatal intestinal macrophages ^[119]. Large bioactive peptides derived from the intestinal digestion of milk OPN in vitro reduce inflammatory responses and maintain an immunological steady state by preventing NF- κ B pathway activation to alleviate intestinal epithelial cell inflammation and enhance barrier function ^[120].

In newborn mice that did not receive LF during lactation, LF supplementation enhances intestinal nutrient digestion and absorption, promotes intestinal development and maturation, and strengthens intestinal barrier function ^[121]. Moreover, rhLF is more effective than bLF. Milk OPN promotes intestinal development in infancy by increasing integrin $\alpha\beta 3$ and CD44 expression, thereby triggering the extracellular signal-regulated kinase (ERK), PI3K/Akt, Wnt, and focal adhesion kinase (FAK) signaling pathways ^[17]. LF and OPN can form a complex that offers strong protection to the intestinal barrier, activates intestinal cell proliferation and differentiation, increases antimicrobial activity, and enhances intestinal maturity more effectively than when LF and OPN are administered separately. The most effective

ratio of LF:OPN was found to be 1:5 (w/w) ^[122, 123]. This complex also slows LF digestion in the infant gastrointestinal tract, preserving or enhancing its biological activity ^[124].

κ -casein is positively associated with *Clostridium butyricum* and is important for early infant intestinal immune system maturation by regulating intestinal flora and further influencing pyruvate metabolic pathways to affect colonic epithelial permeability and reduce inflammatory factor production ^[18]. κ -casein hydrolysis during infant digestion releases GMP, which promotes the growth of intestinal tract bifidobacteria, preventing pathogen colonization ^[125]. LF modulates inflammatory responses and supports immune homeostasis by preserving intestinal epithelial barrier integrity, thereby promoting beneficial bacterial colonization and SCFA production ^[126]. sIgA escorts enteric pathogens and antigens into the gut by targeting microbes and spatially preventing harmful bacteria from adhering to lymphoid tissues for immune cell initiation, protecting neonates from inflammation caused by these pathogens ^[127]. Sialylated mucin also protects intestinal mucus integrity from bacterial degradation and improves intestinal inflammation ^[14].

Mouse Siglec-E (Siglec-10 in humans) is an SA-recognizing inhibitory receptor ^[35]. In vitro osteoclast trials utilizing Siglec-E knockout cells or blocking antibodies against human Siglec-9. This demonstrated that Siglec-E/Siglec-9 suppresses osteoclast resorption activity by negatively regulating the formation of an actin ring, though it does not inhibit differentiation ^[128]. Moreover, LF inhibits osteoblast apoptosis, promotes osteoblast proliferation and differentiation, and suppresses osteoclast development, with bLF exerting a stronger effect than hLF ^[129]. In growing SD rats, daily administration with 1,000 mg/kg LF decreased bone resorption, enhanced bone formation, and improved femoral bone mineral density and trabecular microarchitecture while upregulating the expression of osteocalcin, osterix, and Runx-2, thereby promoting bone health ^[20]. Feeding LF and OPN proteins in a coacervate format increased blood levels of OPN, pro-collagen type 1 N terminal, and macrophage colony stimulating factor, with more significant beneficial effects on bone growth and development ^[124].

4.3 Lipid-bound SA function

During development, large amounts of GAs are present in the hippocampal regions of the brain ^[10]. GT1b and GD1b, the most abundant polysialylated complex GAs in the axonal membrane, have the potential to promote neuronal cell proliferation ^[10]. Maternal supplementation with sea-urchin-derived GAs (SU-GAs) is more effective than GM1 or SA in promoting neurogenesis, dendritic spine growth, and synaptic function in the cortex and hippocampus of mouse pups. This is primarily because SU-GAs upregulate nerve growth factor (NGF) and BDNF expression more efficiently than GM1 and SA ^[130]. In neonatal piglet trials, dietary phospholipids and GAs provided in the form of phospholipid-rich milk protein concentrates improved spatial learning; however, the direct effect of dietary GAs on cognitive development could not be determined ^[131]. Similarly, feeding infants with bovine complex milk fat infant formula containing GD3 (11–12 $\mu\text{g/mL}$) for 6 months resulted in similar levels of neurodevelopment as observed in infants in the breastfed group, with improved cognitive performance in terms of hand-eye coordination and IQ ^[132].

GM3 synthase deficiency (GM3SD) is caused by mutations in the *ST3GAL5* gene, which encodes GM3 synthase, and is characterized by infantile intellectual disability, motor impairment, and epilepsy [133]. Reports indicate that oral GA supplementation improves clinical symptoms, growth and development, and cognitive function in patients with GM3SD [134, 135]. In one study, patients received dairy products rich in GAs (5.5–22 mg/kg/d) for an average of 34 months, but improvements in growth and development were observed only during the first 1–2 months [134]. Moreover, GA supplementation had no effect on serum GA levels. In GM3SD mice, oral supplementation with milk-derived GAs (mainly GM3 and GD3) beginning in the early weaning period improved cognitive decline. However, increased levels of complex GAs (GD1 and GT1) were detected only in the hippocampus of GA-supplemented mice [135].

Zhou and Ward [136] found that fortnight administration of LPS-induced systemic inflammation in mice. Conversely, GA-boosted hepatic gene acetyl-coenzyme A acyltransferase 2 expression and helped maintain intestinal barrier integrity. In vitro assessment of Caco-2 cells revealed that SA enhanced infant resistance to diarrheal episodes and bacterial infections, with free SA (containing GAs) being the most effective, followed by GD3, GM1, and GM3 [137]. In another study, Yan and Su [138] utilized MA104 cells and porcine intestinal epithelial cells to reveal that high concentrations (40 μ M) of GAs with subterminal SA residues, such as GM1a, GD1a, GD1b, and GT1b, demonstrated efficient antiviral activity against RV at 8 and 24 h. Among these, low concentrations of GM1a had a stronger inhibitory effect than the others. However, GM3, a GA containing only one terminal SA, exhibited only a restricted inhibitory effect at 8 h. Effective binding inhibition requires multivalent interactions, which are provided by macromolecules containing multiple SA residues rather than free SA.

The deletion of complex GA (GM2/GD2 and GD3) genes leads to increased bone mass and decreased bone formation and resorption in mice [107]. In human mesenchymal stem cells, GD1a promotes osteoblast differentiation by activating ERK 1/2 MAP kinase and epidermal growth factor receptor (EGFR) phosphorylation, whereas GM3 inhibits osteoblast differentiation by reducing EGFR phosphorylation [139, 140]. Notably, 5 μ M GM3 significantly upregulates the transforming growth factor-beta signaling pathway through SMAD 2/3, inducing chondrogenic differentiation [141]. These findings highlight the key role of GAs in bone health and development.

4.4 Free SA function

Although free SA is scarce and rapidly metabolized, making its utility lower than that of conjugated SA [1, 89], it is a critical component of PSA. Insufficient Neu5Ac impairs PSA synthesis, negatively affecting brain and cognitive development [94]. Animal studies indicate that maternal Neu5Ac supplementation during pregnancy and lactation transfers to the fetus, enhancing cognitive function [142]. Exogenous Neu5Ac improves learning by increasing contents of brain GAs and protein-bound SA when injected intraperitoneally in rat pups, but is not as effective as 6'-SL, possibly because of the faster metabolism and lower bioavailability of free SA [143].

Notably, breast milk Neu5Ac alters the abundance and composition of the gut flora and reduces the risk of obesity in late infancy ^[144]. In high-fat diet-fed rats, dietary Neu5Ac supplementation reduces weight gain, dyslipidemia, and insulin resistance by regulating liver gene transcription, thereby mitigating inflammation and oxidative stress associated with hyperlipidemia ^[145]. Similarly, in mice consuming a high-fat diet, both 3'-SL and Neu5Ac sensibly affect intestinal immunity, digestion, absorption, and circadian rhythm, with 3'-SL showing a more pronounced impact ^[146]. In a mouse brain inflammation model induced by LPS, Qian and Zhang ^[147] found that both EBN and Neu5Ac alleviates organ damage induced by inflammation and improved learning and memory abilities. However, EBN was more effective than Neu5Ac in reducing glial cell activation. In addition, Neu5Ac inhibits LPS-induced inflammation in macrophages and promotes the growth of beneficial gut microbiota, such as *Lactobacillus* and *Bifidobacterium*.

Most of the studies on SA function have relied on in vitro and animal models. The findings of these studies indicate that SA is essential in infant development, with the combination of two SA forms being more efficient. However, few studies have explored the differences in bioavailability of various dietary sources of SA, including oligosaccharides, glycoproteins, GAs, and free SA.

Table 3. Studies on biological functions and molecular mechanisms of SA

Type		Model	Mechanism or pathway outcome	Function
Oligosaccharide form	6'-SL	Mice ^[94]	Adjusts cognitive development; short-term upregulation of genes modulating neuronal patterning in the PFC.	Improves cognitive performance
	6'-SL	Mice and piglets ^[148]	Attenuates NEC inflammation; reduces activated B cell (NF-κB) inflammatory signaling in the intestine.	Anti-necrotizing enterocolitis
	3'-SL	Mice ^[149]	Significantly increases the metabolism of SA in hippocampal tissue and promotes the expression of learning-related genes (<i>NCAM</i> , <i>SCL17A5</i> , <i>ST8SIA4</i> , <i>Gria1</i> , <i>Gria2</i> , <i>Mapk1</i> , <i>Mapk3</i> , <i>FGFR1</i> , and <i>FGFR2</i>).	Improves learning and memory development
	SLs	Preterm pigs ^[98]	Improves spatial cognition; upregulates genes encoding SA metabolism, myelination, and GA biosynthesis.	Improves cognitive performance in preterm pigs
Protein form	CGMP	Piglets ^[112]	Increases learning-associated gene (<i>ST8SiaIV</i> and <i>GNE</i>) expression.	Enhances learning ability and brain development
	LF	Neonatal piglets ^[110]	At low concentrations, the sphingosine-1-phosphate signaling and neurotrophic pathways are significantly upregulated; increases expression levels of BDNF and SLC6A3. At high concentrations, the caveolar-mediated endocytosis and actin cytoskeleton signaling pathways are significantly upregulated; increases expression levels of BDNF and SLC6A3.	Low concentrations enhance neurodevelopment and cognition. Higher concentrations exert greater neuroprotective effects.
	LF	Deoxynivalenol-induced mice ^[126]	Increases jejunal occludin and intelectin 1 protein expression; decreases pro-inflammatory cytokine (IL-1β, IL-6, IL-8, and TNF-α) expression; increases <i>Clostridium XIVa</i> abundance and colonic butyrate concentration.	Alleviates deoxynivalenol-induced intestinal dysfunction

Type		Model	Mechanism or pathway outcome	Function
Lipid form	Milk OPN	Mouse pups, human crypt-like intestinal epithelial cells [17]	Increases the expression of integrin $\alpha\text{v}\beta 3$ and CD44; increases phosphorylation/activation of the ERK, PI3K/Akt, Wnt, and FAK signaling pathways.	Promotes intestinal development during infancy
	Milk OPN	Mice pups [111]	Increases the expression of myelination-related proteins; increases activation of ERK-1/2 and PI3K/Akt signaling.	Promotes early brain development, learning and memory function
	Milk OPN	Preterm pigs [150]	Increases villus-to-crypt ratios across the three small intestinal regions.	Slightly improves intestinal structure and systemic immunity
	sea urchin GAs, GM1	Mice pups and pregnant mice [130]	Promotes the neurodevelopment of young offspring; effectively upregulates the expression levels of NGF and BDNF; promotes neural outgrowth and GAP-43 and MAP-2 expressions of Neuro2a cells.	Promotes neurological development in offspring
	Phospholipids and GAs	Neonatal piglets [131]	Increases concentrations of lactate; decreases concentrations of deoxycarnitine.	Affects brain development and enhances cognition
	GD3	Newborn rat pups [151]	Significantly decreases the incidence and gross/histopathologic severity of NEC; augments mucosal Foxp3 β T-regulatory immune responses.	Protects newborn from NEC
Free form	Neu5Ac	SD rat pups and pregnant SD rats [142]	Maternal Neu5Ac supplementation enhances learning and cognitive performance, and promotes the hippocampus and cortex Neu5Ac content of offspring.	Promotes the cognitive development
	Neu5Ac	High-fat-diet-fed rats [145]	Attenuates weight; significantly increases serum IL-6, and TNF- α levels; decrease mRNA levels of hepatic antioxidant genes.	Attenuates inflammation and oxidative stress

5. SA Against PTB

5.1 SA supplementation during pregnancy to prevent PTB

During pregnancy, immune imbalance becomes more prevalent in the third trimester than in earlier stages, increasing the risk of pregnancy-related complications [23]. Therefore, it is essential to identify high-risk pregnancies and provide timely interventions. Recently, SA has been investigated in studies on PTBs (Figure 4).

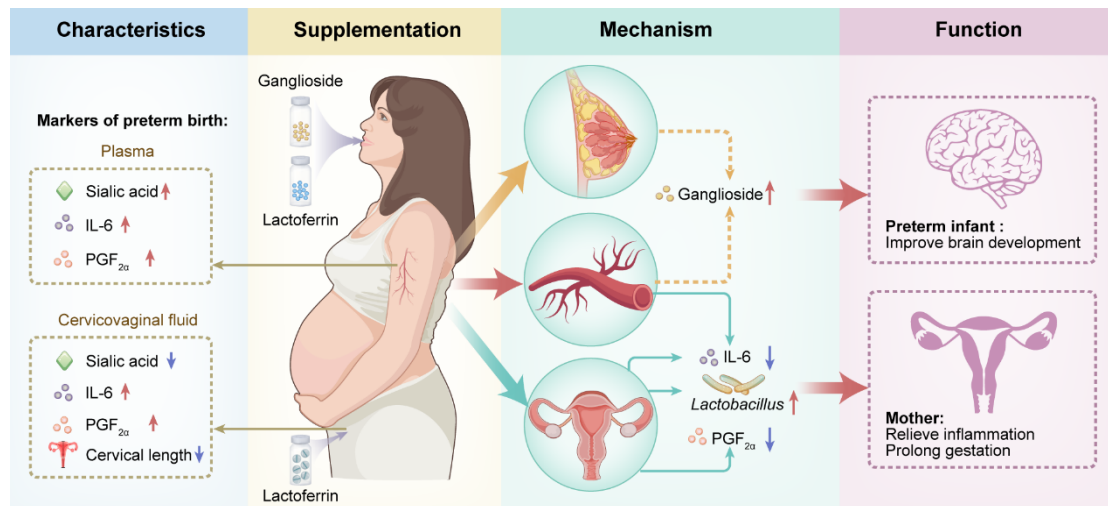


Figure 4. Role of different forms of SA in the prevention of PTB. Gangliosides have been shown to promote brain development, and oral administration of gangliosides to pregnant women at risk of PTB may increase ganglioside levels in breast milk (dashed arrow), thereby supporting infant neurodevelopment. Clinical studies have confirmed (solid arrow) that supplementing lactoferrin—either orally or vaginally—in pregnant women at risk of PTB can effectively prevent further cervical shortening and increases in fetal fibronectin, thereby prolonging gestation. SA, Sialic acid; PTB, preterm birth; IL-6, interleukin-6; PGF_{2α}, prostaglandin F_{2α}.

5.1.1 Oligosaccharide-bound SA

Oligosaccharide-bound SA is in the amniotic fluid as early as the beginning of the second trimester [33]. Preterm infants, especially those born very preterm, may miss crucial weeks of oligosaccharide-bound SA nutrition in the amniotic fluid [152]. Supplementation with probiotics such as *Bifidobacterium lactis*, *B. infantis*, and *Lactobacillus acidophilus* in pregnancies at risk of PTB has been shown to increase 3'-SL content in breast milk by 50%, strengthening the mucosal barrier and acting as an anti-inflammatory agent to help prevent infections. This may improve both short- and long-term health outcomes [153].

Oligosaccharide-bound SA, especially 3'-SL, is positively correlated with cervicovaginal pro-inflammatory factors, and is associated with a short cervix, heightened inflammation, and PTB [154]. PTB may upregulate SA production systems earlier, potentially leading to increased production of sialylated HMOs in preterm breast milk [55]. These characteristics could help identify women at risk for PTB, thus enabling more personalized interventions. There are two distinct processes that modulate the risk of PTB [155]: one is linked to aseptic inflammation and is marked by elevated serum 3'-SL levels; the other is microbiome-mediated and involves a lower ratio of 3'-SL to 6'-SLN in urine. Thus, assessing oligosaccharide-bound SA levels during pregnancy could yield significant insights regarding the causes of PTB, even in women who show no obvious symptoms. However, further research is required to determine whether oligosaccharide-bound SA in serum, urine, or amniotic fluid during early pregnancy could serve as a reliable predictive marker for PTB, helping to develop new interventions targeted at improving the health of both mothers and babies.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection increases the risk of PTB and stillbirth [156]. Pregnant women infected with SARS-CoV-2 during the second and third trimesters exhibit lower levels of α2,3 galactose-linked SA and higher levels of PSA in the trophoblast and underlying

basement membranes of the placenta compared with that of healthy pregnant women and those infected earlier in gestation ^[157]. These placental alterations may contribute to pregnancy complications and adversely affect pregnancy outcomes. Additionally, α 2-6 bond-linked SA compounds can bind to the SARS-CoV-2 spiny S1 subunit and block viral adhesion to host cells, suggesting that 6'-SL may help prevent SARS-CoV-2 infections ^[158].

5.1.2 Protein-bound SA

Numerous clinical studies (Table 4) in pregnant women at risk of PTB have evaluated the impact of LF on perinatal inflammatory challenges, intrauterine growth restriction, and iron deficiency (ID) anemia (IDA). Infection/inflammation is widely recognized risk factor for PTB. In pregnant women with IDA at risk of PTB, 1 month of continuous oral recombinant hLF (rhLF) treatment results in the normalization of vaginal flora (disappearance of vaginal infections) and suppression of vaginal inflammatory responses ^[159]. A study of 11 preterm pregnant women with ID or IDA who received a combination of oral and vaginal rhLF for 4 weeks showed promising results ^[160]. The treatment led to reduced levels of IL-6 in both cervicovaginal fluid and serum, as well as decreased PGF_{2 α} levels in cervicovaginal fluid. These changes helped prevent cervical shortening and fetal fibronectin elevation, prolonging gestation. In addition, similar findings were reported in a group of 128 women at risk (shortened cervix) of PTB, with 64 pregnant women who supplemented 300 mg of vaginal LF for 21 consecutive d experiencing reduced cervicovaginal IL-6 secretion and increased cervical length compared with untreated controls. Thus, oral or vaginal administration of LF may prevent PTBs in pregnant women ^[161].

Bacterial vaginosis (BV) is an imbalance of multiple microorganisms in the vaginal microbiota, which breaks down and consumes the SA-containing mucus components in the vagina. Therefore, this weakens the protective and immune functions of mucus and increases the risk of PTB ^[162]. Several clinical trials have shown that LF supplementation (oral 150 mg/d and intravaginal 700 mg/d) in patients with refractory BV and previous recurrent PTBs significantly improved vaginal microbiota composition ^[163, 164]. These patients delivered at term without complications. A recent study of patients with refractory BV and previous recurrent PTBs showed that supplementation with 300 mg of vaginal LF daily for 21 d reduced the risk of PTB ^[165]. Thus, LF may be particularly beneficial for high-risk cases of PTB, probably owing to its anti-inflammatory effect.

In summary, although the sample sizes in these studies were small, LF shows potential for clinical applications in preventing PTBs, especially in high-risk pregnancies. Further large-scale and robust randomized controlled trials are essential to clarify the actual role of LF in mitigating the risk of PTB and influencing perinatal outcomes in high-risk women.

Table 4. Clinical benefits of LF for pregnant woman at risk of PTB

Type	Intervention (way, dosage, and time)	Study participant (quantity and age)	Outcome	Conclusion
rhLF	Oral, 200 mg/d,	$n = 21$, 22–36 years	Vaginal microflora (vaginal infection)	bLF prolongs the length

Type	Intervention (way, dosage, and time)	Study participant (quantity and age)	Outcome	Conclusion
[159]	1 month	IDA, at risk of PTB	disappearance) normalization and reduced IL-6 levels in cervicovaginal fluid.	of pregnancy in pregnant women at risk of PTB with IDA.
bLF [160]	Oral, 200 mg/d, Intravaginal, 100 mg/8 h, 4 weeks	n = 161, 20–40 years ID/IDA, at risk of PTB	Oral administration: Increased RBC, Hb, TSI, and sFtn levels, along with a consistent decrease in serum IL-6 levels. Oral and intravaginal administration: Increased RBC, Hb, TSI, and sFtn levels, reduced IL-6 levels in both serum and cervicovaginal fluid, decreased cervicovaginal PGF _{2α} , and suppression of uterine contractility. Prevented cervical shortening and fetal fibronectin.	bLF administration prolongs the length of pregnancy and prevented PTB.
LF [161]	Intravaginal, 300 mg/d, 21 d	n = 128, at risk of PTB	Decreased IL-6 levels and increased cervical length.	LF may benefit women at risk of PTB by addressing shortened cervical length and elevated IL-6 levels.
bLF [163]	Oral, 150 mg/d, Intravaginal, 700 mg/d, 1 month	n = 6, 30–39 years, BV	Lactobacillus appeared and gradually became dominant; five patients delivered healthy infants at term.	bLF administration prevents refractory vaginitis, cervical inflammation, and PTB.
bLF [164]	Oral, 150 mg/d, Intravaginal, 700 mg/d, 1 year	n = 1, 38 years, refractory vaginitis	Lactobacillus appeared and gradually became dominant; woman delivered a healthy infant.	bLF is effective in patients with refractory bacterial vaginosis who experience recurrent PTB.
LF [165]	Intravaginal, 300 mg/day, 21 d	n = 125, 27.6 ± 6.0 years, BV, prior spontaneous PTB	Lower rate of PTB (25%), lower mean gestational age at delivery (37.7 ± 3.2 weeks), and lower rate of admission.	LF supplementation in women with BV in the first trimester of pregnancy may reduce the risk of PTB.

Abbreviations: bLF, bovine lactoferrin; BV, bacterial vaginosis; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia; LF, lactoferrin; PTB, preterm birth; rhLF, recombinant human lactoferrin; sFtn, serum ferritin; TSI, total serum iron.

5.1.3 Lipid-bound SA

Currently, research on GA supplementation during human pregnancy is limited. A first double-blind controlled trial evaluated a complex milk-fat-based formula containing high doses of GAs (≥ 4 or 8 mg/d) during pregnancy. Compared with the low-dose control group, the high-dose supplementation increased total GA and GM3 levels in both maternal serum and breast milk [166].

However, no significant differences were observed between the supplemented group and controls who did not consume dairy products, nor did supplementation affect PTB risk. This lack of effect may be attributed to insufficient GA dosage to elicit meaningful physiological changes.

GA levels in the infant brain normally rise rapidly in the third trimester [10]. In preterm infants, however, brain GA stores are relatively low [167]. Animal studies show that supplementing pregnant and lactating rats with GAs significantly increases total brain GA concentrations and offspring brain weight at high doses [168]. However, maternal supplementation does not improve long-term behavioral or cognitive outcomes. Therefore, clinical trials are needed to determine whether dietary GA

supplementation—particularly in early pregnancy for women at risk of PTB—can enhance embryonic brain development and later intellectual performance. Although GD3 and GM3 are the predominant GAs in human milk, they represent only a small fraction of brain GAs and are not ideal as supplements. Instead, GD1a or GT1b may be more suitable during pregnancy (16–30 weeks) ^[167].

5.2 SA and preterm infant development

SA levels in the breast milk of mothers with preterm infants fluctuate throughout lactation but remain consistently higher than those in term infants, supporting the specific growth and developmental needs of preterm infants. Supplementation of preterm infants with different forms of SA early in life compensates for the nutritional deficiencies during lactation in terms of cognitive ability, intestinal immunity, and growth and development (Table 5).

5.2.1 Improvement of cognitive abilities

Postnatal nutrition, especially with SA, is significant for neurodevelopment in preterm infants. The high contents of SA in both maternal serum and breast milk from the second trimester to 1-month post-partum can promote early intellectual development in infants ^[12]. However, breast milk from preterm mothers may not provide sufficient nutrition for their infants. Experimental results of dietary SA supplementation in preterm pigs showed that preterm pigs supplemented with SL approached the cognitive levels of the corresponding full-term pigs ^[98], whereas preterm pigs supplemented with OPN showed no effect on cognitive function ^[150].

An investigation of the impact of oral GA supplementation on brain function in 2,230 children with cerebral palsy showed that GA treatment improved neurological symptoms, particularly muscle tension, limb mobility, language abilities, and cognitive development, leading to more rapid improvements in younger children (0–3 years) ^[169]. Although this population did not include preterm infants, PTB is a known risk factor for cerebral palsy. Thus, GAs may help compensate for the cognitive and neurological deficits often associated with PTB. In addition, in a study of sudden infant death syndrome, most breastfed infants had significantly higher content of GA and protein-bound Neu5Ac in the outer frontal lobe membranes and better brain development than formula-fed infants ^[11]. Supplementing bovine milk fat globule membrane (SA-rich) to formula-fed infants aged 2–6 months resulted in significantly higher cognitive scores compared with those fed conventional infant formula at 12 months. This supplementation also closed the cognitive development gap between formula-fed and breastfed infants ^[170]. Therefore, the role of GAs in the development of brain function in preterm infants and optimal timing of their effects should be further explored and clarified.

Regrading preterm infants, donor breast milk is commonly utilized when maternal milk is unavailable or insufficient. However, feeding nutritionally fortified, pasteurized donor breast milk did not improve neurodevelopment in very preterm infants aged 22–26 months compared with those fed preterm formula ^[171]. Notably, the protein and energy content of donor milk is lower than that of breast milk ^[172]; for example, pasteurization affects LF ^[173], OPN ^[174], and bile salt-stimulated lipase (BSSL) ^[175, 176] contents in

breast milk. Atayde and Kapoor ^[177] studied 36 preterm infants born at < 32 weeks of gestation and found that LF exposure during hospitalization was linked to greater gray matter and total brain volumes. Growth in the gray matter volume occurs predominantly in the third trimester; therefore, the growth rate of brain regions in the third trimester may be influenced by LF. In summary, the effectiveness of donor milk in supporting neurodevelopment in preterm infants can be impacted by factors such as inadequate milk dosage, improper processing and storage, and variations in SA composition compared with maternal breast milk.

5.2.2 Regulation of intestinal immunity

Preterm infants miss the crucial third trimester transplacental nutrient transfer, making optimal enteral feeding essential for their growth and development. The high concentrations of sIgA in colostrum provides preterm infants with essential immune factors and aids in the absorption of high-molecular-weight proteins in the gastrointestinal tract ^[53]. In addition, sIgA binds to potentially harmful bacteria in the intestines of preterm infants. The presence of IgA in the feces of very preterm breastfed infants by the first week of life, compared with its appearance in formula-fed preterm infants only by the third week ^[21, 178], emphasizes the significance of colostrum and its sIgA content.

Aasmul-Olsen and Henriksen ^[150] demonstrated that OPN-active proteins in cow's milk improve intestinal development and protect the gut in preterm pigs. Additionally, exogenous bLF regulates intestinal proteins in preterm pigs. Specifically, low doses (0.1–1 g/L) may help stimulate intestinal maturation by inducing IEC proliferation, whereas high doses (10 g/L) may adversely affect apoptosis and inflammation ^[179]. Preterm infants supplemented with bLF, particularly those receiving probiotics, exhibited greater microbiota diversity than those without bLF, along with significant reductions in *Lactobacillus* and *Staphylococcus* ^[180]. However, supplementing preterm infants with bLF alone had little effect on the development of their gut microbiota, possibly because the duration of LF treatment was too short to be effective ^[181]. Furthermore, GMP binds to pathogenic bacteria, promotes the growth of beneficial bacteria, and exerts many biological effects on intestinal health. Formulas fortified with scGOS/lcFOS (9:1) and GMP are beneficial for preterm infants and promote the growth of intestinal bifidobacteria in preterm infants ^[125].

In addition, GA supplementation in preterm infant formula promotes the growth of *Bifidobacterium* and inhibits the growth of potentially pathogenic microorganisms in the intestinal tract of preterm neonates, suggesting that GAs is instrumental in the development of the preterm infant intestinal tract ^[182]. Future attempts should be made to compare the differences in intestinal development in preterm infants fed breastfed and GA formulas. Oligosaccharide-bound SA alters the intestinal flora of neonates and reduces the ability of these bacteria to infect them; however, no clinical studies have been conducted in preterm infants.

5.2.3 Enhancement of growth and development

SA levels increased with decreasing gestational age and were negatively correlated with birth weight and length. However, the decrease associated with longer breastfeeding time was not significant after day 120, suggesting that high contents of SA in breast milk may contribute to early preterm growth ^[40].

Moreover, 3'-SL and 6'-SL were positively correlated with higher fat-free mass percentage and larger head circumference, respectively, in discharged preterm infants, but were not associated with weight gain independently. This suggests a possible beneficial impact of sialylated HMOs on growth and development [183]. Subsequently, examination of preterm infants' feces for the relationship between gut flora and growth and body composition revealed that *Clostridium_sensu_stricto_1* in the gut was positively correlated with obesity, with a negative correlation between 6'-SL, 3'-SL, and DSLNH and *Clostridium_sensu_stricto_1* abundance [184]. Therefore, sialylated HMOs may help regulate body composition in preterm infants. Qng and Cherkerzian [185] found that high sialylated HMO content has a minimal effect on growth and development, though it offers other health benefits. Nevertheless, a longitudinal comparison of growth in large preterm cohorts is needed, as differences in study design and analytical approaches may explain the similar findings.

A phase 2 clinical trial found that supplementing preterm infants with recombinant human BSSL (rhBSSL) enhanced growth owing to improved lipid digestion and absorption compared to that of a placebo. However, no meaningful association was found between the impact of rhBSSL on growth velocity and coefficient of fat absorption. Therefore, the mechanism behind rhBSSL's action may be more complex than simply enhancing total fat absorption [175]. In a broader, longer phase 3 pilot study, rhBSSL supplementation benefited a subgroup of preterm infants with lower gestational ages [176]. This suggests that rhBSSL supplementation could be particularly beneficial for specific populations, including preterm infants with higher energy needs. However, an optimal feeding regimen for rhBSSL has yet to be established. Oral nutritional supplements with LF (400 mL/d) in 12–60-month-old infants with infection-induced growth retardation improves immunity by increasing IL-6/IL-10 ratios and balancing IL-6 and IL-10 levels to increase infant weight and body length [186]. Supplementation with LF in preterm infants with impaired growth or low birth weight remains a key area of research.

5.3 SA supplementation for PTB combats preterm infant diseases

Preterm newborns who miss late-gestation nutrient transfer experience physiological immaturity that impairs the development of multiple organ systems—including the lungs, intestines, and brain—resulting in neurodevelopmental deficits such as cognitive, neurological, and sensory impairments (Figure 5) [21, 22, 177]. Numerous trials have shown that SA supplementation helps reduce the risk of neonatal diseases (Table 5) [125, 187].

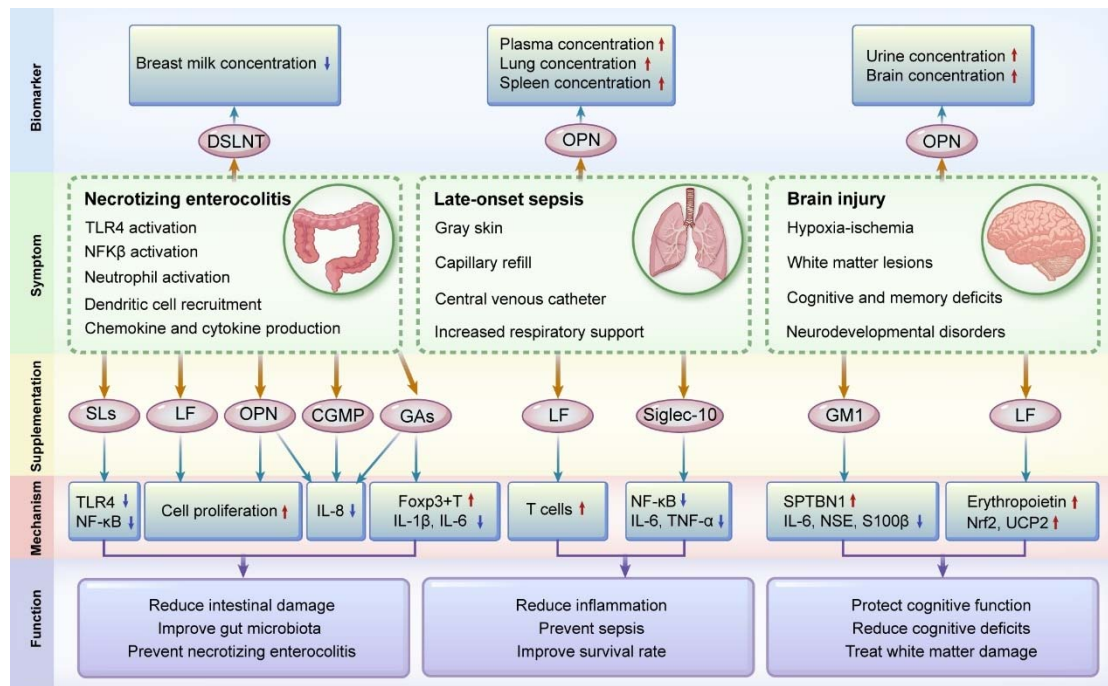


Figure 5. Role of different forms of SA in the prevention and treatment of preterm infant diseases. Conjugated SA provides protective effects against necrotizing enterocolitis, late-onset sepsis, and brain injury in preterm infants. **A** High concentrations of DSLNT in breast milk are associated with NEC risk in preterm infants. SLs inhibit NEC development by suppressing the TLR4/NF-κB pathway, whereas GAs, OPN, and CGMP reduce inflammatory factor expression and alleviate NEC-related inflammation. **B** LF suppresses inflammation by regulating the balance of T helper cells. CD24 binds damage-associated molecular patterns and Siglec-10, inhibiting the damage-associated molecular pattern-mediated NF-κB activation via activation of the tyrosine phosphatase SHP-1, thereby reducing pro-inflammatory cytokine production. **C** LF and GM1 support and protect brain development, reducing neurobehavioral dysfunction. DSLNT, disialyllacto N-tetraose; OPN, osteopontin; SLs, sialyllactoses; LF, Lactoferrin; CGMP, casein glycomacropeptide; GAs, gangliosides; Siglec-10, SA-binding immunoglobulin-like lectin 10; GM1, Monosialoganglioside 1; TLR4, Toll-like receptor 4; NF-κB, nuclear factor-kappa B; IL, interleukin; TNF-α, tumor necrosis factor-alpha; SPTBN1, spectrin beta, non-erythrocytic 1; NSE, neuron specific enolase; S100β, central nervous system specific protein β; Nrf2, Erythroid 2-related factor 2; UCP2, Uncoupling protein 2.

Table 5. Clinical benefits of SA in preterm infants

Form	Treatment (way, dosage, and time)	Study participant (quantity and age)	Outcome	Conclusion
GMP ^[125]	Enteral feeding, 40 mg/100 mL SA, 28 d	<i>n</i> = 72, 32.4 ± 1.3 weeks	Abundance of <i>Bifidobacterium</i> was significantly increased.	Formula enriched with scGOS/lcFOS (9:1) and GPM is beneficial to the intestinal microecology of VPT infants.
rhBSSL ^[175]	Oral, 150–180 mL/kg/d, 1 week	<i>n</i> = 63, 1.3–7.6 years	Mean growth velocity significantly improved by 2.93 g/kg/day; the risk of suboptimal growth decreased to 30% (< 15 g/kg/day).	rhBSSL treatment is well tolerated and significantly improves growth and LCPUFA absorption.
rhBSSL ^[176]	Oral, 22.5–27 mg/kg/d, 4 weeks	<i>n</i> = 415, 1–8.4 years	Higher incidence of adverse events; Predefined subgroup: growth velocity improved.	In small-for-gestational-age infants, rhBSSL significantly improves growth.
bLF ^[180]	100 mg/d, 1 month	<i>n</i> = 29, 0–48 h	Infant receiving bLf supplementation had higher overall species richness in the microbiome.	bLF supplementation has minimal impact on microbiota composition/function in preterm infants receiving probiotics.

Form	Treatment (way, dosage, and time)	Study participant (quantity and age)	Outcome	Conclusion
bLF ^[181]	Enteral feeding, 5 d	<i>n</i> = 479, 5 d	NICU: levels of three unidentified stool metabolites and acetic acid significantly higher.	bLF supplementation has minimal impact on the gut microbiome or metabolome.
bLF ^[188]	Oral, 100 mg/d, 30 d	<i>n</i> = 472, born	Decrease in LOS was significant in VLBW (< 1,000 g) neonates; decrease occurred for threshold retinopathy, bacterial, and fungal episodes.	bLF supplementation alone or in combination with probiotics reduces the incidence of a first episode of LOS in VLBW neonates.
bLF ^[189]	Oral, 200mg/d, 7–29 d	<i>n</i> = 25, throughout hospitalization	Fewer sepsis episodes were observed in infants; individual increases in Treg levels were higher.	LF prophylaxis reduces nosocomial sepsis episodes.
bLF ^[190]	Oral, 200 mg/kg/d, 4 weeks	<i>n</i> = 190, 0–1 month	Overall sepsis occurred less frequently (12.6%).	bLF supplementation prevents LOS in low-weight preterm infants.
bLF ^[191]	Enteral feeding, 100, 200, and 300 mg/kg/d, 30 d	<i>n</i> = 31, 21 d	One bloodstream infection occurred in each group, no urinary tract infection, and no cases of NEC.	bLF at doses up to 300 mg/kg/day are safe in preterm infants.
GAs ^[182]	Enteral feeding or oral, 1.80 ± 0.16 mg/kg/d, 30 d	<i>n</i> = 43, 0–48 h	Bifidobacterial counts in feces were higher; the relative content of <i>Escherichia coli</i> in feces was significantly lower.	GAs alter fecal flora and promote intestinal immunity.
GM1 ^[187]	Intravenous drip, 20 mg/d, 14, 28, or 42 d	<i>n</i> = 76, 28–36 weeks	Significantly lower incidence of complications; marked reduction in IL-6, NSE, and S100β levels.	GA supplementation supports preterm infants with white matter damage and reduces complications.

Abbreviations: bLF, bovine lactoferrin; GAs, gangliosides; GMP, glycomacropeptide; LCPUFA, long-chain polyunsaturated fatty acid; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; NICU, neonatal Intensive care unit; NSE, neuron specific enolase; rhBSSL, recombinant human bile salt-stimulated lipase; VPT: very preterm infants; VLBW, very low birth weight.

5.3.1 NEC

NEC is a common disease in preterm infants, associated with an imbalance in intestinal flora, especially pathogenic microorganisms such as *Enterobacteriaceae* ^[21]. In a preterm cohort study, lower concentrations of DSLNT were found in the breast milk of mothers whose infants developed NEC. Furthermore, preterm infants whose mothers had higher DSLNT levels in their milk showed a higher abundance of beneficial bacteria and lower abundance of harmful bacteria ^[192]. Studies indicate that DSLNT is a non-invasive predictive biomarker for identifying infants at risk of NEC ^[193]. Thus, its concentration in breast milk may help predict neonatal susceptibility to NEC. In addition, SLs prevent NEC development by preventing the activation of the TLR-4/NF-κB signaling pathway in animal models, including piglets, rats, and mice ^[148, 194]. However, SLs alone, particularly 3'-SL, have limited effectiveness in promoting robust bifidobacteria colonization and may not sufficiently counteract the deleterious effects of pure formula feeding or PTB on the immune system and intestinal barrier ^[195].

In a trial of very preterm infants, enteral supplementation with bLF (150 mg/kg/d; maximum 300 mg/d) did not diminish NEC incidence ^[196]. Notably, LF administration (100 mg/d) had no negative effects and was associated with reduced hospitalization ^[197]. However, in extremely low birth newborns, the

combination of bLF and probiotic *L. rhamnosus* GG reduced the incidence of stage 2 or more severe NEC compared with that of bLF alone [188]. Moller and Thyman [198] found that while feeding preterm piglets with OPN formula did not reduce NEC incidence, it significantly reduced its severity. Moreover, OPN and CGMP improved intestinal lactase activity and reduced IL-8 secretion in the intestinal epithelial cells of preterm pigs [199]. Currently, studies investigating protein-bound SA in relation to NEC are limited. Nevertheless, further randomized trials and studies involving larger groups of infants are needed to determine whether it reduced NEC severity in preterm infants.

The use of dietary GD3 in neonatal rats with NEC revealed that GD3 (15 µg/mL) protects neonatal rats from NEC to some extent by enhancing mucosal Foxp3⁺ T-regulated immune responses [151]. Using an NEC model involving *E. coli* LPS and intestinal tissues from hypoxic preterm infants, Schnabl and Larsen [200] demonstrated that GAs protect the infant gut by modulating vasoactive mediators and inhibiting pro-inflammatory signaling, including IL-1β, IL-6, and IL-8 signaling. In a randomized clinical trial, the incidence of NEC was lower in very preterm infants fed donor breast milk compared with those fed preterm infant formula [171]. In summary, the best method to prevent and treat NEC in preterm infants remains the provision of breast milk [193, 195, 201].

5.3.2 LOS

Neonatal sepsis is categorized into two forms: early onset sepsis, which typically presents after birth, and LOS, occurring > 72 h after birth and prior to hospital discharge [188]. Low-birth-weight and/or preterm infants are the primary risk factors for LOS, with common manifestations including improved respiratory support, delayed capillary refill, gray skin, and the presence of central venous catheters [22]. The levels of OPN in the lung, spleen, and plasma of patients with sepsis are significantly elevated and positively correlated with disease severity and mortality rate [202, 203]. In a sepsis mouse model, knocking out the *Opn* gene reduces TNF-α and IL-6 levels. OPN depletion affects bacterial clearance ability by inducing intestinal antimicrobial peptide production and the AKT–FOXO3a signaling pathway, thereby affecting sepsis prognosis and improving the survival rate [204]. OPN has the potential to serve as a biomarker in LOS; however, studies in preterm infant cohorts are scarce. In the future, large-scale clinical cohort studies should be conducted to explore the combined use of OPN with other biomarkers, such as suPAR and HMGB1, to enhance diagnostic accuracy and prognostic evaluation.

Initially, Manzoni and Rinaldi [188] showed that administering 100 mg/kg/d of bLF orally decreased the incidence of the first episode of LOS in very-low-weight preterm infants. A placebo-controlled, double-blind trial found that preterm infants have lower levels of T-regulatory cells compared with those of full-term infants. Elevated T-regulatory cell levels were observed with oral LF (200 mg/d) prophylaxis, which may be the mechanism underlying the protective effect of LF against sepsis [189]. Subsequently, Ochoa and Zegarra [190] revealed that oral administration of 200 mg/d of LF reduced the number of septicemia episodes in preterm infants with low-birth-weights. Ochoa and Loli [205] further research found that bLF was more effective in protecting very low-birth-weight preterm infants with delayed sepsis. A

prospective dose-escalation safety study of bLF showed that oral administration of 300 mg/kg/d bLF was safe for preterm infants ^[191]. Specifically, bLF was shown to effectively inactivate microorganisms causing sepsis in recovered infant formula and bacterial growth media, leading early researchers to believe that bLF could prevent neonatal sepsis ^[206]. However, several recent large cohort studies found that LF supplementation did not notably decrease the incidence of LOS in preterm infants or had only minimal effects ^[181, 196, 197]. Differences in infection prevention measures and exposure to other interventions may explain these contrasting outcomes.

Mouse Siglec-G (Siglec-10 in humans) is expressed predominantly on B-1a cells to maintain homeostasis in vivo ^[207]. In sepsis, extracellular cold-inducible RNA-binding protein causes the downregulation of Siglec-G expression and decrease of B-1a cell number in the peritoneal cavity ^[208]. On the surface of DCs, CD24 binds damage-associated molecular patterns and Siglec-G, forming a trimolecular complex that causes the inhibition of damage-associated molecular pattern-mediated NF- κ B activation via activation of SHP1, resulting in decreased production of pro-inflammatory cytokines ^[209, 210]. Tan and Reilly ^[210] employed a small decoy peptide protecting Siglec-G to inhibit neutrophils aiding B-1a cell migration. Specifically, the interaction of Siglec-G with CXCL12 or CXCR4 regulates B-1a cell migration to alleviate inflammation and improves sepsis survival rate. This suggests that Siglec-G maintains B-1a cell homeostasis and has the potential to improve sepsis prognosis. Despite its critical immunomodulatory function, the regulation of sepsis in preterm infants via Siglec-10 remains unexplored.

5.3.3 Hypoxic-ischemic

Perinatal cerebral hypoxic-ischemia frequently causes brain injury and is highly prevalent in preterm infants with neurodevelopmental deficits, often leading to severe damage and long-term sequelae ^[167]. LF has been demonstrated to be effective in resolving cerebral hypoxia-ischemia in models of preterm infants ^[211, 212]. rhLF injected into rat dams during gestation or lactation rescued cognitive deficits induced by perinatal hypoxia and improved various memory types in juvenile and adult rats via upregulating erythropoietin expression ^[213]. In an LPS-induced rat inflammatory brain injury model, supplementing maternal LF during lactation exhibited neuroprotective effects on preterm rats ^[211]. Specifically, it reduced ventriculomegaly, brain tissue loss, and myelination deficits. Optimal effects were achieved in rat dams at a dose of 1 g/kg; nevertheless, administration at 10 g/kg resulted in reduced brain volume, increased astrocyte proliferation, and hypomyelination ^[212]. Carvalho and Sanches ^[214] supplemented pregnant rats with LF (1 g/kg) during lactation. Hypoxic-ischemic rat pups breastfed by these mothers showed reduced oxidative stress and enhanced mitochondrial function, mediated by increased expression of nuclear factor erythroid 2-related factor 2 and uncoupling protein 2 at 6 and 24 h, improving neonatal hypoxic-ischemic injury. However, the appropriate dosage, benefits, and potential risks of LF administration in clinical practice still need further exploration.

Cerebral white matter myelin defects in infants with GM1 deposition are believed to result from axonal loss and delayed myelin formation. In a rat model of ischemic brain injury, GM1 was administered at 60

mg/kg/d via tail vein injection for 2 weeks. The results showed that GM1 alleviated neurological damage, inflammation, and apoptosis in the ischemic parietal cortex of rats by increasing SPTBN1 levels ^[215]. In a clinical study of 76 preterm infants, treatment with intravenous GM1 for 14 d resulted in significant reductions in periventricular white matter damage 7 and 14 d after birth compared to that of a control group receiving the standard of care. After 1 year, children in the GA-treated group exhibited superior motor, language, and social adaptation skills compared with that of controls ^[187]. Currently, GM1 is widely used to treat neonatal hypoxic-ischemic diseases.

In a mouse model of hypoxia-ischemia-induced preterm brain injury, endogenous OPN expression was significantly increased in the brain, with OPN-derived C154-198 and N134-153 peptides exacerbating brain injury. OPN administration did not have any protective effect against brain injury in PTBs ^[216]. Subsequently, Nilsson and Baburamani ^[217] demonstrated that OPN expression is significantly increased in areas of white matter injury after death in preterm infants, which may contribute to the inflammatory process following white matter injury. Few studies have explored the diagnosis and treatment of brain injury in preterm infants, highlighting the need for further research to investigate the beneficial effects of breast milk-derived OPN on brain structure and function under the inflammatory conditions commonly experienced by preterm infants. Although hypoxia and ischemia are widely regarded as major contributors to white matter injury, their underlying mechanisms remain poorly understood.

5.3.4 Other diseases

Biomarkers such as OPN can predict acute kidney injury (AKI) in preterm infants. In most preterm infants, urinary OPN concentrations show a negative correlation with body weight and gestational age. Additionally, male infants have higher contents of OPN in their urine than female infants ^[218]. However, no single biomarker currently covers all AKI diagnoses. Treatment with an OPN-neutralizing antibody significantly reduced mouse plasma IL-6, IL-1 β , and MIP-2 levels, and even lowered the levels of some organ damage biomarkers, thereby protecting against acute lung injury (ALI) during sepsis ^[203]. Recently, SA alleviates ALI symptoms, improves pulmonary edema, and reduces inflammation by regulating the NF- κ B and MAPK pathways ^[219]. Further clinical studies in preterm infants are required to confirm the efficacy of SA in preventing and treating AKI and ALI.

6. SA Safety

According to genetic toxicology and subchronic toxicology studies, no rat deaths were observed after oral administration of 20 g/kg 3'-SL or 6'-SL, the highest dose ^[220, 221]. In newborn animals, the unobservable adverse effect dose of 3'-SL was determined to be 5 g/kg/d in rats ^[220] or 1.2 g/kg/d in piglets ^[195]; The unobservable adverse effect dose of 6'-SL is 1200 mg/L in piglets ^[222]. Infant formula containing five oligosaccharides (2'-FL, 3-FL, LNT, 3'-SL, and 6'-SL) formulated to mimic human milk, demonstrated that 0.2 g/L of 3'-SL and 0.3 g/L of 6'-SL supported normal growth gastrointestinal tolerance, and safe use in healthy full-term infants ^[223]. In addition, 3'-SL, 6'-SL, and GOS (7.3 ± 1.0 g/100 g) have been shown to be safe for the growth and development of infants ^[224].

Clinical studies have shown that adding LF to infant formula is safe and well-tolerated ^[114, 191]. Healthy full-term infants fed formula containing bLF (0.6 or 1.0 g/L) demonstrated good tolerance and safety over a 365-d period ^[113, 225]. LF is now widely incorporated into infant formulas, although its intake is strictly regulated. We found that the highest concentrations of infant formula can reach up to 468 mg/100 g LF. In clinical trials involving preterm or low birth weight infants, higher doses are often used; for example, bovine LF administered at up to 300 mg/kg/d has been shown to be safe in preterm infants ^[191].

At present, no authoritative institution has defined or recommended intake levels for lipid-bound SA. Studies indicate that infant formula is the primary dietary source of GA, accounting for ~85% of intake, with concentrations ranging from 0.03 to 11.4 mg/100 g ^[48]. In a double-blind, randomized, controlled, parallel group clinical trial, adding 2–3 mg/100 g GD3 to infant formula and feeding infants for 6 months supported developmental outcomes comparable to those of breastfed infants, with no adverse effects observed ^[132]. In a cohort of preterm infants, supplementation with an average of 1.80 ± 0.16 mg/kg/d of GAs in formula for 30 consecutive d was also confirmed to be safe ^[182].

In a safety assessment using the human-identical milk monosaccharide Neu5Ac to simulate natural intake, Sprague–Dawley pregnant rats received free Neu5Ac at 974 or 1246 mg/kg/d with no compound-related adverse effects on female reproduction, offspring development, or growth ^[226]. In another study, newborn mice were administered SA twice a day (240 mg/kg/d) for 14 d without any impact on body weight or growth rate ^[90].

7. Conclusions and Prospects

SA is an essential nutrient that supports early-life growth, development, and health, particularly by enhancing cognitive function and regulating the gut microbiota. It also provides additional benefits, including antibacterial, antiviral, anti-inflammatory, and immunomodulatory effects, and contributes to brain development. Moreover, conjugated SA shows potential in preventing NEC and in treating LOS and ischemic–hypoxic brain injury.

Currently, SLs and LF have been approved for use in infant formula by both the US Food and Drug Administration (FDA) and European Food Safety Authority (EFSA). According to GRN 921, 3'-SL sodium salt may be added to infant formula at concentrations up to 0.28 g/L. Likewise, 6'-SL and its sodium salt are permitted in non-exempt, full-term infant formula at levels up to 0.4 g/L (GRNs 881 and 922). EFSA has confirmed that the maximum allowable level of bLF in infant formula is 1000 mg/L, whereas the FDA permits up to 100 mg/100 g of lactoferrin. Major infant-formula manufacturers, including Abbott and Wyeth, now include 3'-SL, 6'-SL, and LF in their products. In 2016, the FDA also approved Neu5Ac as an enzyme-based ingredient for full-term infant formula with a maximum level of 50 mg/L (GRN 602). Despite these approvals, the concentration of SA in commercial infant formulas remains substantially lower than that of breast milk. Therefore, some products now include free Neu5Ac to help increase SA levels and better approximate the composition of human milk. However, the absorption efficiency and bioavailability of free SA are lower than those of conjugated SA.

At present, many questions remain regarding the application of SA in infant formula, maternal nutrition, and clinical practice.

(1) Mothers of preterm infants have significantly higher SA concentrations in their breast milk than mothers of full-term infants. Dietary SA supplementation does not appear to increase breast milk SA levels, suggesting that these changes may reflect a self-regulatory mechanism to support infant growth and development [5]. However, the underlying mechanism remains unclear.

(2) Milk and milk-based infant formulas contain small amounts of Neu5Gc. Human and animal studies indicate that dietary Neu5Gc from red meat and dairy products may contribute to inflammatory diseases [1]. As humans cannot synthesize Neu5Gc, further research is needed to determine whether long-term consumption of Neu5Gc-rich foods poses health risks.

(3) The rate-limiting bifunctional enzyme GNE has low activity in newborn rat pups [75], suggesting that infants—particularly preterm infants—may also have limited capacity for endogenous SA synthesis. Evidence indicates that dietary SA can be absorbed and incorporated into metabolic pathways [1, 30]. However, key questions remain: What is the metabolic fate of dietary SA in infants? Which forms are most efficiently absorbed? When endogenous SA production is insufficient, to what extent can exogenous sources and salvage pathways compensate? How do the relative contributions of endogenous synthesis, dietary intake, and salvage SA differ across tissues during early life?

(4) Most current studies on SA function rely on animal or in vitro models and typically assess only one or two forms of SA, with a narrow focus on intestinal or brain effects. Comprehensive comparative studies evaluating multiple SA forms within the same model are lacking. Critical knowledge gaps include the specific developmental mechanisms whereby different SA forms influence the brain and intestine, which forms exert the greatest impact on cognitive development, and the largely unexplored roles of sialylated glycoproteins and glycolipids.

(5) Sialylated components in human milk are considered natural therapeutic or preventive biomolecules, yet clinical trials in pregnant women and newborns are limited and primarily focus on preterm infants or associated conditions. More clinical studies are needed to evaluate the benefits of SA supplementation for infant neurological and gastrointestinal development. Although multiple trials of LF supplementation have been conducted in pregnant women and preterm infants, results vary widely. Therefore, further research is required to determine optimal dosage, timing of supplementation, and appropriate clinical endpoints for evaluating efficacy.

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Disclosure of interest

The authors report there are no competing interests to declare.

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