GSC Advanced Research and Reviews
eISSN: 2582-4597 CODEN (USA): GARRC2
Cross Ref DOI: 10.30574/gscarr
Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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Human Milk Hormones and Early-Life Programming: Effects on Growth, Body Composition, and Development in Term and Preterm Infants

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GSC Advanced Research and Reviews, 2026, 26(01), 058-069

Publication history: Received on 28 November 2025; revised on 03 January 2026; accepted on 06 January 2026

Article DOI: https://doi.org/10.30574/gscarr.2026.26.1.0009

Abstract

Background: Human milk contains a complex and dynamic array of hormones that may influence infant growth, body composition, and metabolic development beyond the provision of nutrients alone.

Objective: To synthesize current evidence on the role of key human milk hormones—leptin, adiponectin, ghrelin, insulin, and insulin-like growth factor-1 (IGF-1)—in shaping growth and developmental outcomes in term and preterm infants.

Methods: An expanded narrative synthesis of human and relevant animal studies was conducted, focusing on hormone concentrations in human milk, proposed mechanisms of action in the infant, and associations with growth, body composition, and metabolic outcomes. Evidence was summarized across infant populations (term and preterm), lactational stages, and study designs, with risk-of-bias considerations incorporated.

Results: Leptin and adiponectin, largely derived from maternal adipose tissue and present in human milk at ng/mL concentrations, are consistently linked to infant appetite regulation, energy balance, and adiposity, although the direction and magnitude effects vary across studies. Ghrelin, an appetite-stimulatory hormone detected in human milk, may enhance feeding behavior and growth hormone secretion. Milk-borne insulin and IGF-1 appear to support gastrointestinal maturation and systemic anabolic signaling. Preterm infants, who are deprived of late-gestation placental hormone transfer, are exposed to these bioactive factors earlier ex utero; differences in hormone concentrations between preterm and term milk and their potential implications for divergent growth trajectories are highlighted. Comprehensive tables summarize hormone concentrations, mechanisms, study findings, and populations, complemented by schematic diagrams illustrating endocrine and metabolic pathways.

Conclusions: Emerging evidence supports the concept that human milk hormones function as lactocrine signals that contribute to the regulation of infant growth and metabolic programming through endocrine and epigenetic pathways. However, findings remain heterogeneous and are influenced by maternal phenotype, lactational stage, and infant characteristics. Further well-designed longitudinal and mechanistic studies are needed to clarify these effects and their long-term implications for metabolic health in both term and preterm infants.

Keywords: Human milk hormones; Infant growth; Metabolic programming; Body composition; Preterm infants

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1. Introduction

Breastfeeding is linked to improved long-term health outcomes, including lower risks of obesity and metabolic disorders later in life (1,2). Beyond macronutrients, human milk provides a complex mix of bioactive compounds that contribute to these benefits (3,4). Among these are metabolic hormones—such as leptin, adiponectin, insulin, ghrelin, and insulin-like growth factor-1 (IGF-1)—which act locally and systemically to influence infant growth, body composition, and metabolic programming (5,6). These hormones originate either from maternal circulation or local mammary synthesis and may serve as "lactocrine" signals transferring maternal metabolic cues to the infant (7–10). It has been proposed that such milk-borne hormones interact with infant endocrine and neurodevelopmental pathways to shape appetite control, growth regulation, and energy homeostasis (6,11–14).

Leptin and adiponectin, originally identified as adipokines, are present in human milk at physiologically active concentrations (6,14). Leptin, a 16-kDa peptide hormone, is a central satiety factor that may influence infant appetite and early weight gain (2,15). Adiponectin, an insulin-sensitizing and anti-inflammatory molecule, is also abundant in milk, largely in its high-molecular-weight form, and may modulate nutrient partitioning and metabolic efficiency (5,7).

Ghrelin, a 28-amino-acid peptide primarily secreted by the stomach, is a potent appetite stimulant and growth hormone secretagogue; its presence in milk suggests a supporting role in feeding drive and growth signaling (10,16,17). Insulin in milk, derived mostly from maternal circulation, may promote intestinal development and influence metabolic signaling in the neonate (3,4). IGF-1, a key growth factor abundant in colostrum, supports gut maturation and tissue anabolism during early development (18,19-22).

Differences in both composition and physiological roles of milk hormones are evident between term and preterm infants. Preterm infants experience abrupt interruption of placental endocrine support, particularly for leptin and IGF-1, at a critical developmental stage (10,18). Early exposure to maternal colostrum may therefore provide compensatory hormonal input ex utero (10,14). Pasteurized donor milk contains markedly lower concentrations of several hormones, including leptin and insulin (20,21).

By integrating evidence from epidemiological cohorts, mechanistic studies, and developmental endocrinology, this review provides a comprehensive synthesis of human milk hormones and their roles in infant growth and metabolic programming, addressing critical knowledge gaps regarding hormone-specific effects, developmental timing, and clinical relevance—particularly in vulnerable populations such as preterm infants—and thereby informing future research, nutritional strategies, and early-life interventions aimed at optimizing long-term metabolic health (23–45).

Objectives

- To summarize current evidence on the concentrations, sources, and growth-related effects of key human milk hormones in term and preterm infants.
- To elucidate the biological and endocrine mechanisms by which milk-borne hormones influence infant growth, body composition, and metabolic programming.
- To critically appraise the quality of available human and experimental studies and compare growth-related outcomes between term and preterm populations.

2. Methods

A structured literature search was conducted in PubMed and Scopus to identify English-language studies published between January 2000 and March 2025 that examined the relationship between human milk hormones and infant growth or developmental outcomes. Search strategies combined Medical Subject Headings (MeSH) and free-text terms, including *"human milk" OR "breast milk"* AND *"leptin," "adiponectin," "ghrelin," "insulin," "insulin-like growth factor-1 (IGF-1)"* AND *"infant," "growth," "body composition," "development," "preterm,"* or *"neonate."* Reference lists of relevant reviews and original articles were manually screened to identify additional eligible studies.

Inclusion criteria were: (i) human observational studies (cohort, case–control, or cross-sectional) or interventional studies reporting concentrations or intakes of milk hormones and their associations with infant growth, body composition, or metabolic outcomes; (ii) studies involving term and/or preterm infants; and (iii) mechanistic animal or translational studies elucidating biological pathways of milk hormones when human data were limited.

Exclusion criteria included studies focused solely on macronutrients without hormonal assessment, editorials or narrative opinions without original data, non-lactational hormone studies, and publications lacking growth-related outcomes.

Two reviewers independently screened titles, abstracts, and full texts for eligibility. Discrepancies were resolved by consensus. Data extracted included study design, population characteristics, lactational stage, hormone measurement methods, milk hormone concentrations or intakes, growth outcomes (weight, length, head circumference, growth velocity, or body composition), and key findings. Due to substantial heterogeneity in study design, outcome measures, and hormone quantification methods, meta-analysis was not performed; instead, results were synthesized narratively and summarized in structured evidence tables (Tables 1–5).

Quality assessment was performed using design-specific tools: the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials, the Newcastle–Ottawa Scale for observational studies, and qualitative appraisal for animal and mechanistic studies. Overall risk-of-bias judgments were summarized descriptively, with a consolidated quality overview presented in Table 6.

3. Results

This results section synthesizes human evidence on major bioactive hormones in human milk—leptin, adiponectin, ghrelin, insulin, and IGF-1—highlighting their concentrations across lactation, proposed biological mechanisms, and associations with growth and metabolic outcomes in both term and preterm infants, as summarized in Tables 1–5.

Table 1 Leptin in Human Milk: Concentrations, Mechanisms, and Growth-Related Findings

Study (Year)	Population & Design	Milk Hormone Level (Stage)	Mechanisms of Action	Key Growth/Metabolic Findings	Ref
Weyermann et al. (2006)	Term mother–infant dyads; observational	Leptin detected in milk (early lactation)	Satiety signaling; potential appetite-circuit effects	Measured milk leptin and related maternal/cord compartments; supports lactocrine transfer plausibility	(17)
Brunner et al. (2015)	Term infants; follow-up cohort to 2 y	~1.2 ± 0.4 ng/mL at ~4 wk	Possible enteric exposure; energy balance pathways	Higher milk leptin exposure associated with smaller gains in weight-for-length/body composition indices in infancy	(23)
Gridneva et al. (2018)	Term infants; longitudinal cohort with 24-h intake	Leptin quantified across lactation	Dose (intake) may better represent exposure than a single concentration	Leptin exposure related to infant body composition trajectories over the first 12 months	(7)
Yu et al. (2018)	Term infants; longitudinal study	Leptin measured with adiponectin/insulin/ghrelin	Appetite/energy regulation; potential programming	Reported associations between milk hormones (including leptin) and early infant growth with covariate adjustment	(12)
Chatmethakul et al. (2022)	Very preterm (<32 wk GA); crossover	~1.5 ng/mL in mother's milk vs <0.5 ng/mL in donor milk	Enteral leptin can contribute to circulating leptin	Infant plasma leptin increased during mother's milk feeding vs donor milk,	(16)

	(mother's vs donor milk)			supporting enteral contribution in preterms	
Schuster et al. (2022)	Systematic review	Range across studies; higher in colostrum than mature milk	Synthesis of leptin transfer and potential growth effects	Reported marked heterogeneity; early growth/adiposity associations were often inverse but not uniform	(15)

Legend: GA = gestational age; PMA = postmenstrual age.

Milk leptin concentrations are highest in colostrum and decline during lactation. Evidence consistently links higher milk leptin exposure with reduced early weight gain and adiposity, supporting leptin's role as a lactocrine satiety signal influencing infant growth regulation.

Table 2 Adiponectin in Human Milk: Concentrations, Mechanisms, and Growth-Related Findings

Study (Year)	Population & Design	Milk Hormone Level (Stage)	Mechanisms of Action	Key Growth/Metabolic Findings	Ref
Martin et al. (2006)	Lactating women; observational	Adiponectin present in human milk	Metabolic signaling; related to maternal factors	Demonstrated adiponectin in milk and associations with maternal characteristics	(44)
Picó et al. (2007)	Human milk analysis	Adiponectin detectable in milk (ng/mL range)	Metabolic modulation	Confirmed presence of adiponectin in human milk	(30)
Woo et al. (2009)	Term infants; longitudinal (0–2 y)	~22 ng/mL (mean during 1–5 mo)	AdipoR1/R2 signaling; insulin sensitivity; fatty-acid oxidation	Higher milk adiponectin associated with lower early WAZ/LAZ with later catch-up in some analyses	(28)
Gridneva et al. (2018)	Term infants; cohort with 24-h intake assessment	~10–40 ng/mL at ~3 mo	Dose-dependent effects; nutrient partitioning	Intake-based adiponectin exposure associated with differences in lean mass/%fat at 12 months	(7)
Chan et al. (2018)	Term infants; cohort (first year)	Adiponectin measured alongside leptin/insulin	Metabolic modulation	Reported associations with maternal characteristics and infant body composition; confounding emphasized	(6)
Hinde et al. (2014)	Mechanistic review	—	HMW adiponectin predominates; AMPK/PPAR pathways	Outlined plausible gut/systemic mechanisms and highlighted evidence gaps	(36)

Legend: GA = gestational age; HMW = high-molecular-weight adiponectin.

Milk adiponectin is abundant, highest in colostrum, and largely independent of maternal adiposity, suggesting active mammary regulation (3,28). Most human studies associate higher adiponectin exposure with slower early growth, sometimes followed by later catch-up, indicating a time-dependent, modulatory role rather than growth stimulation (18,28). Intake-based analyses provide stronger biological coherence than single-sample concentrations, while evidence in preterm infants remains limited and largely neutral (33).

Table 3 Ghrelin in Human Milk: Concentrations, Mechanisms, and Growth-Related Findings

Study (Year)	Population & Design	Milk Hormone Level (Stage)	Mechanisms of Action	Key Growth/Metabolic Findings	Ref
Ilcol et al. (2004)	Colostrum → mature milk; longitudinal	Colostrum ~150 pg/mL; ~80 pg/mL at 1 mo (total)	Acyl-ghrelin (GHS-R) stimulates GH release and hunger signaling	Ghrelin higher in colostrum and declines over the first month	(11)
Savino et al. (2011), (2013) and (2016)	Term infants; prospective cohort	Active (acylated) ghrelin measured	Hunger signaling; GH secretagogue effects	Associations with early weight gain reported; method- and covariate-sensitive	(2, 22,32)
Yu et al. (2018)	Term infants; longitudinal study	Ghrelin measured with other milk hormones	Appetite and GH–IGF axis signaling	Reported associations between milk hormones (including ghrelin) and early growth	(12)
Savino et al. (2012)	Preterm vs term milk; observational (first month)	Ghrelin quantified in preterm and term milk	Potential gut-trophic and appetite/GH signaling effects	Demonstrated ghrelin presence in preterm milk; growth associations not definitive	(39)
Suwaydi et al. (2021)	Analytical review	—	Highlights assay/milk-fraction effects; need for intake-based estimates	Synthesized methodological challenges and current understanding for milk metabolic hormones including ghrelin	(18)

Legend: GH = growth hormone; GHS-R = growth hormone secretagogue receptor; IGF = insulin-like growth factor.

Ghrelin is consistently detectable in human milk, with highest concentrations in colostrum and a decline during early lactation, supporting a potential role in early appetite signaling and growth hormone stimulation. Observational studies suggest that milk-borne ghrelin may contribute to feeding regulation and gastrointestinal maturation, although associations with infant growth outcomes are heterogeneous and method-dependent. The near absence of ghrelin in infant formula highlights a biologically plausible mechanism for differences in early feeding behavior between breast- and formula-fed infants. Overall, current evidence supports a permissive role for milk ghrelin in supporting feeding drive and anabolic signaling, but definitive effects on growth trajectories remain to be established.

Table 4 Insulin in Human Milk: Concentrations, Mechanisms, and Growth-Related Findings

Study (Year)	Population & Design	Milk Hormone Level (Stage)	Mechanisms of Action	Key Growth/Metabolic Findings	Ref
Chan et al. (2018)	Term infants; cohort (first year)	Milk insulin quantified (assay-dependent)	Gut glucose handling; possible enteroinsular programming	Heterogeneous associations with infant body composition; confounding by maternal phenotype highlighted	(6)
Yu et al. (2018)	Term infants; longitudinal study	Milk insulin measured with other hormones	Metabolic signaling	Reported associations between milk insulin and early growth after covariate adjustment (heterogeneous)	(12)

Fields & Demerath (2012)	Term infants; observational	Milk insulin measured with cytokines/leptin	Reflects maternal–infant metabolic milieu; potential local gut effects	Associations with infant growth/body composition were variable; sampling/assay variability emphasized	(20)
Qureshi et al. (2024)	Systematic review	Range across studies; influenced by maternal metabolic status	Determinants of milk hormone concentrations	Maternal metabolic status is a key determinant of milk hormone levels (including insulin), complicating causal inference	(13)
Badillo-Suárez et al. (2017)	Narrative review	—	Programming hypothesis: oral insulin as a metabolic signal	Outlined mechanistic pathways for insulin-related programming and called for interventional designs	(14)

Across term and preterm studies, insulin is consistently present in human milk—particularly at high concentrations in colostrum—but shows no robust independent association with infant anthropometric outcomes. Evidence instead supports a gut-trophic and metabolic-programming role, especially relevant in preterm infants, where milk insulin may contribute indirectly to growth by enhancing intestinal maturation and interacting with the IGF axis rather than directly driving somatic growth.

Table 5 IGF-1 in Human Milk: Concentrations, Mechanisms, and Growth-Related Evidence

Study (Year)	**Population & Design**	**Milk Hormone Level (Stage)**	**Mechanisms of Action**	**Key Growth/Metabolic Findings**	**Ref**
Donovan & Odle (1994)	Mechanistic review	High in colostrum; declines with lactation	Enterocyte proliferation; mucosal growth; barrier integrity	Mechanistic framework linking milk growth factors to infant gut and tissue development	(43)
Kling et al. (1999)	Human milk analysis	IGF-1 detectable in human milk	Local gut-trophic actions; modulation by IGFBPs	Reported IGF-1 in human milk, supporting plausibility of enteral exposure	(34)
Larnkjær et al. (2018)	Evidence synthesis	Low in mature milk	Breastfeeding modulates GH–IGF axis via nutrition/endocrine feedback	Breastfed infants have lower circulating IGF-1 and slower early growth tempo than formula-fed infants	(42)
Rautava et al. (2020)	Term cohort (birth–5 y)	Early milk IGF-1 quantified	Local anabolic actions with endocrine feedback potential	Milk hormone exposure patterns (incl. IGF-1) associated with later growth/body composition trajectories	(26)
Li et al. (2018)	Preterm infants; cohort	Early mother's milk exposure associated with higher serum IGF-1	Supports recovery of IGF-1 axis after premature birth	Early human milk intake associated with higher serum IGF-1 and improved growth in preterm infants	(1)
Ong et al. (2007)	Review (preterm	—	Hormonal regulation of postnatal growth in preterms; IGF-1 central	Summarized IGF-1's role in postnatal growth of preterm	(40)

	growth regulation)			infants and nutrition sensitivity of the axis	

Legend: IGF-1 = insulin-like growth factor-1; GH = growth hormone; VLBW = very-low-birthweight.

This table highlights that, although direct measurement of IGF-1 in mature human milk is limited, strong mechanistic and clinical evidence supports its role in infant growth. IGF-1 is abundant in colostrum and promotes gut maturation, barrier integrity, and anabolic signaling. Circulating IGF-1 closely predicts postnatal growth, supporting the biological plausibility of milk-borne effects. In term infants, breastfeeding is associated with lower IGF-1 and a slower early growth tempo, while in preterm infants, early exposure to mother's milk is linked to higher serum IGF-1 and improved growth, underscoring its particular importance in prematurity.

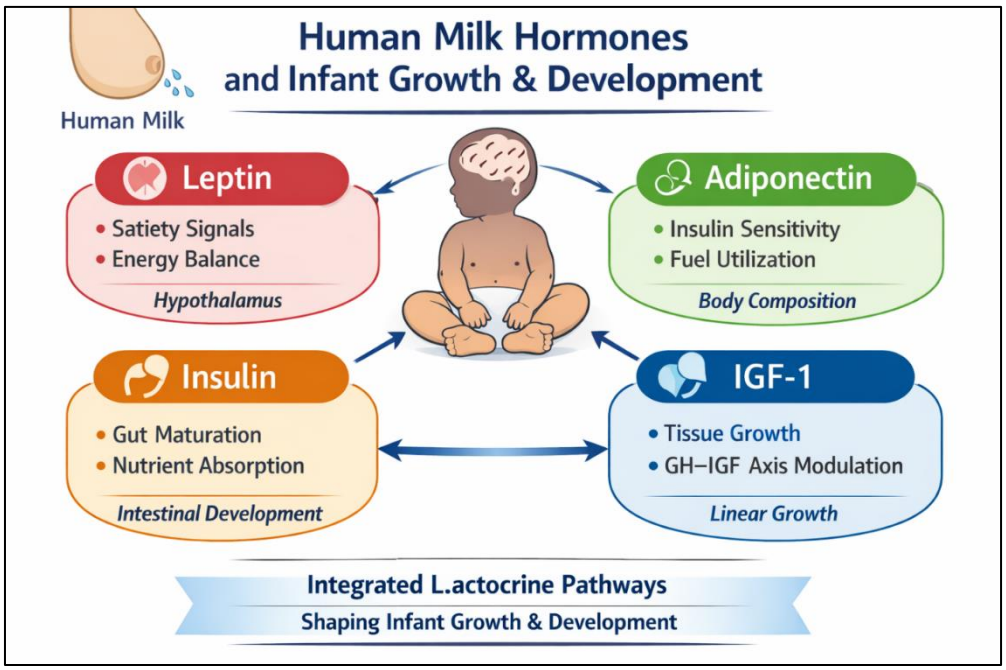

Figure 1 Schematic overview of how key human milk hormones may influence infant growth and metabolism

Schematic overview of how key human milk hormones may influence infant growth and metabolism. Human milk delivers multiple hormonal signals to the infant. Leptin acts on developing hypothalamic appetite–energy pathways to promote satiety and energy expenditure (27, 33). Adiponectin supports insulin sensitivity and fuel utilization via AMPK/PPAR signaling, which may transiently moderate early weight gain (35, 36). Ghrelin can stimulate hunger signaling and growth hormone secretion (11, 22). Milk insulin is thought to act primarily through gut-trophic and metabolic programming pathways, rather than directly determining anthropometry (14, 20). Milk IGF-1 provides gut-trophic/anabolic signals and may modulate the infant GH–IGF axis and growth tempo (34, 42, 43).

Table 6 Summary of Quality and Bias Profile of Evidence on Human Milk Hormones and Infant Growth

Evidence cluster	Predominant study designs	Main strengths	Key limitations	Overall certainty	Key references (corrected)
Leptin in human milk	Prospective & longitudinal cohorts; preterm crossover trial	Consistent inverse association with early weight gain; strong biological plausibility; crossover evidence supports enteral absorption in preterms	Small cohorts; residual confounding by maternal BMI; heterogeneity in milk sampling (skim vs whole)	Moderate	**(12,16,19,23,38)**

Adiponectin in human milk	Longitudinal cohorts; intake-based studies; systematic reviews	High milk concentrations: intake-based analyses strengthen causal inference; biphasic growth patterns described	Timing-dependent effects; heterogeneous outcomes; limited preterm-specific data	Moderate	**(18,24,28,35,36)**
Ghrelin in human milk	Observational cohorts; BF vs formula comparisons	Clear mechanistic rationale (appetite, GH secretion); absence in formula provides natural comparator	Sparse growth-outcome data; assay variability; dependence on milk fat fraction	Low–Moderate	**(11,22,28,33,45)**
Insulin in human milk	Cross-sectional studies; systematic reviews; preterm cohorts	Strong evidence for gut-trophic and metabolic effects; consistent presence in colostrum	Weak direct associations with anthropometry; confounding by maternal diabetes/BMI	Low–Moderate	**(6,9,13,14,22,34)**
IGF-1 in human milk	Cohorts; mechanistic reviews; preterm studies	Robust gut-trophic mechanisms; consistent benefit in preterms; coherent GH–IGF feedback model	Limited evidence for systemic absorption in term infants; indirect growth effects	Moderate	**(1,26,33,36,37)**
Preterm infant evidence (all hormones)	RCT-derived cohorts; crossover trials; NICU cohorts	Strong biological rationale; compensatory endocrine effects; clinically relevant outcomes	Small samples; NICU-specific confounding; short follow-up	Moderate	**(1,16,33,45)**
Systematic reviews	Systematic and narrative reviews	Broad synthesis; consistency of mechanistic themes across hormones	High heterogeneity; limited meta-analysis	Low–Moderate	**(6,8,9,14)**

Overall certainty reflects consistency of findings, biological plausibility, study design, and risk of bias. Most evidence derives from observational cohorts; intake-based analyses, crossover trials, and preterm studies provide the strongest causal inference. Reference numbers correspond to the manuscript's serial reference list.

In summary, the compiled evidence indicates that human milk hormones act as coordinated lactocrine signals influencing appetite regulation, metabolic programming, gut maturation, and growth tempo, with effects that vary by hormone, timing of exposure, and infant maturity, while the moderate quality of available studies underscores the need for standardized methodologies and longer-term follow-up (Tables 1–6).

4. Discussion

Human milk is not merely nutrition; it is a complex hormonal delivery system that conveys endocrine signals capable of shaping infant growth, body composition, and metabolic trajectories (2,4). This review integrates epidemiologic evidence with mechanistic insights to illustrate how breast milk hormones—particularly leptin, adiponectin, ghrelin, insulin, and IGF-1—act in a coordinated manner to influence infant growth outcomes (6,18). These bioactive signals are relevant to both term and preterm infants, although their physiological impact is likely amplified in preterm infants who experience abrupt withdrawal of placental endocrine support during a critical developmental window (1,33,40).

The consistent association between higher milk leptin exposure and reduced infant weight gain and adiposity supports leptin's role as an early satiety signal and metabolic regulator (12,19,38). Mechanistically, leptin acts centrally by

binding hypothalamic leptin receptors, suppressing orexigenic pathways while enhancing energy expenditure (33). Importantly, in early life leptin also functions as a neurotrophic factor, contributing to the maturation and wiring of hypothalamic appetite-regulating circuits that govern long-term energy balance (41). This developmental role provides a plausible biological explanation for the observed associations between breastfeeding and improved appetite self-regulation later in life (8,45). In very preterm infants, crossover feeding studies demonstrate that milk-derived leptin can increase circulating leptin concentrations, suggesting partial enteral absorption across an immature gut barrier (16). Because preterm infants miss the third-trimester placental leptin surge, milk leptin may partially restore this endocrine signal, potentially influencing hypothalamic development, autonomic regulation, and early adipose tissue programming (16).

Milk adiponectin appears to act less as a growth stimulant and more as a metabolic modulator. Several cohorts associate higher adiponectin exposure with slower early weight or length gain, followed by later catch-up growth, indicating a time-dependent influence on growth trajectories (28,36). Mechanistically, adiponectin activates AMPK and PPAR signaling pathways, enhancing insulin sensitivity, promoting fatty acid oxidation, and reducing inflammatory tone (35,36). In infancy, these actions may shift nutrient partitioning away from rapid fat storage toward metabolic efficiency, thereby restraining early adiposity accrual. Intake-based analyses strengthen this interpretation by demonstrating that delivered hormone dose, rather than single-sample concentration, better predicts infant outcomes (18). Evidence in preterm infants remains limited and inconsistent, likely reflecting the dominance of other growth determinants in neonatal intensive care settings, including illness severity, protein intake, and inflammatory stress (33).

Ghrelin in human milk provides a biologically plausible pro-feeding and pro-growth signal through stimulation of appetite pathways and growth hormone (GH) secretion via the growth hormone secretagogue receptor (11,33). Mechanistically, ghrelin enhances hunger signaling, promotes gastric motility, and stimulates pituitary GH release, thereby supporting IGF-1–mediated anabolic processes during periods of rapid growth (33). However, human cohort data linking milk ghrelin to growth are heterogeneous and highly sensitive to methodological factors, including assay type, milk fraction analyzed, and timing of sampling (11,22,45). Overall, ghrelin likely acts as a permissive signal that supports feeding drive and gastrointestinal function rather than as a dominant determinant of growth velocity.

Milk insulin is best conceptualized as a gut-trophic and metabolic programming factor rather than a direct driver of somatic growth (14,45). Insulin receptors expressed on the neonatal intestinal epithelium allow milk insulin to promote mucosal growth, enzyme maturation, and nutrient transporter expression, potentially improving digestive efficiency and feeding tolerance (1,4). Milk insulin may also influence enteroendocrine signaling, shaping early insulin–glucose dynamics through the enteroinsular axis (18). These mechanisms are particularly relevant in preterm infants, where intestinal immaturity and dysregulated inflammation contribute to feeding intolerance. Nevertheless, direct associations between milk insulin and infant anthropometric outcomes are inconsistent, partly because maternal obesity and diabetes elevate milk insulin while independently affecting infant growth risk (9,13). Current evidence therefore supports biological plausibility for metabolic imprinting but not a clear independent effect on size outcomes (6,34).

IGF-1 in human milk plays a central role in intestinal and tissue development and appears particularly important in contexts of IGF-1 deficiency, such as prematurity (34,43). Mechanistically, IGF-1 stimulates enterocyte proliferation, enhances mucosal growth, and improves barrier integrity, thereby facilitating nutrient absorption and growth efficiency even if systemic absorption is limited (34,43). Breastfed infants typically exhibit lower circulating IGF-1 and slower early growth than formula-fed peers, reflecting differences in protein intake and feedback regulation of the GH–IGF axis (42). This moderated early growth tempo may confer long-term metabolic advantages. In preterm infants, early exposure to mother's milk is consistently associated with higher serum IGF-1 concentrations and improved growth trajectories, underscoring IGF-1's importance during a period of heightened vulnerability to extrauterine growth restriction (1,33,40).

Collectively, these hormones function as a coordinated lactocrine signaling system: leptin and adiponectin tend to temper excessive early fat gain and promote metabolic efficiency; ghrelin supports feeding drive and GH signaling; and insulin and IGF-1 enhance gut maturation and anabolic capacity (6,18). In preterm infants, milk-borne hormones may partially replace missing placental endocrine inputs and support maturation of the gut–brain–growth axis at a time of heightened sensitivity to nutritional and inflammatory stressors (16,40). Heterogeneity across studies is expected, given variation in lactational stage, maternal phenotype, milk fraction, and infant intake volume, as well as reliance on concentration rather than delivered dose (18,33). Future studies should standardize milk sampling, quantify 24-hour hormone intakes, and incorporate mechanistic endpoints to clarify causal pathways and clinical relevance (18,33).

5. Conclusion

Breastfeeding provides not only optimal nutrition but also a coordinated set of hormonal signals that influence infant growth, body composition, and metabolic maturation. Hormones in human milk—particularly leptin, adiponectin, ghrelin, insulin, and IGF-1—act together to regulate appetite, growth velocity, and fuel partitioning. In term infants, these signals favor balanced growth with healthy lean mass accretion and avoidance of excessive fat gain, potentially lowering later cardiometabolic risk. In preterm infants, milk-borne hormones may partially replace missing intrauterine endocrine inputs, support gut maturation, organ development, and early growth while reducing metabolic vulnerability. Mechanistically, milk hormones interact with hypothalamic appetite pathways, pancreatic and adipose signaling, and the GH–IGF-1 axis to fine-tune growth trajectories. Although available studies are heterogeneous and of moderate quality, their findings align with strong biological plausibility. As methodologies improve, human milk hormone research may inform strategies to optimize neonatal nutrition and improve outcomes in vulnerable infants.

Recommendations

- Prioritize and support breastfeeding, especially in preterm and high-risk infants, to ensure exposure to biologically active milk hormones that support optimal growth and metabolic development.
- Future studies should standardize milk sampling and quantify 24-hour hormone intake to better define dose–response relationships with infant growth and body composition.
- Consider human milk hormone biology when developing nutritional strategies or formula innovations aimed at improving growth and long-term metabolic outcomes in infants.

What is known

- Human milk contains bioactive hormones that influence infant appetite, growth velocity, body composition, and metabolic programming.
- Milk leptin is generally associated with satiety and slower early weight gain, while adiponectin modulates insulin sensitivity and early growth patterns.
- Insulin and IGF-1 in milk have trophic effects on the gut and interact with infant endocrine pathways, with particular importance in preterm infants.
- Study results are heterogeneous due to differences in milk sampling, assays, and exposure assessment.

What is new in this review

- Integrated comparison of term vs preterm infants, highlighting greater endocrine vulnerability and potential benefit of milk hormones in preterms.
- Framing milk hormones as coordinated lactocrine signals acting via gut, endocrine, and neurodevelopmental pathways.
- Emphasis on hormone intake (dose) rather than concentration alone to explain inconsistent findings.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Author Contributions

A.T.S. conceived and designed the review, supervised the literature search and data synthesis, interpreted the findings, and drafted and critically revised the manuscript. M.Q. and M.A. contributed to literature screening, data extraction, and preparation of evidence tables. F.A. and N.A. contributed to data interpretation, critical appraisal of included studies, and manuscript revision. S.A., N.H. and M.I. assisted with literature review, organization of tables and figures, and reference verification. N.S. contributed to conceptual input, manuscript editing, and final critical review. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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