World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Maternal characteristics, milk-borne IGF-1, and neonatal growth: Insights into endocrine and developmental programming

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World Journal of Advanced Research and Reviews, 2025, 28(01), 1494-1507

Publication history: Received on 11 September 2025; revised on 18 October 2025; accepted on 20 October 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.28.1.3574

Abstract

Background: Human milk contains a dynamic array of bioactive hormones and growth factors that extend beyond nutrition to influence neonatal growth, metabolism, and developmental programming. Among these, insulin-like growth factor-1 (IGF-1) is a pivotal mediator of tissue anabolism, gut maturation, and postnatal adaptation. Maternal metabolic and obstetric factors modify the concentration of IGF-1 and related hormones in milk, shaping infant growth trajectories from birth through early childhood.

Objectives

- To examine how maternal characteristics—including body mass index (BMI), adiposity, gestational diabetes mellitus (GDM), and delivery mode—affect IGF-1 and associated milk hormones (insulin, leptin, adiponectin, ghrelin).
- To evaluate the impact of milk-borne IGF-1 on neonatal, preterm, and early-childhood growth outcomes.
- To explore mechanistic pathways linking maternal endocrine status, milk hormonal composition, and infant developmental programming.

Methods: A structured literature search was performed in PubMed, Scopus, and Web of Science through March 2025. Eligible studies included human cohorts, case–control, and randomized trials reporting milk IGF-1 levels in relation to maternal factors or infant outcomes. Data extraction included sample characteristics, timing of milk collection, hormonal assays, and growth indices. Study quality was assessed using the Newcastle–Ottawa Scale and Cochrane RoB-2 tools. Results were synthesized descriptively due to heterogeneity across designs.

Results: Twenty-two studies met inclusion criteria. Maternal obesity and diabetes were consistently associated with elevated milk IGF-1 and insulin but reduced adiponectin and obestatin, enhancing early postnatal weight gain. Cesarean delivery and social stress were linked to lower IGF-1 levels, while early breastfeeding in preterms significantly increased serum IGF-1 and promoted catch-up growth. Experimental supplementation with enteral IGF-1 improved intestinal integrity but did not accelerate weight gain. Longitudinal cohorts revealed a biphasic effect: higher early milk IGF-1 correlated with increased infant weight at 1 year but reduced BMI at 3–5 years, reflecting adaptive metabolic programming. Pasteurization of donor milk decreased IGF-1 bioactivity by ~40%, underscoring the benefit of mother's own milk.

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Conclusions: Maternal metabolic health, nutritional status, and perinatal factors critically determine milk IGF-1 bioavailability and its impact on neonatal growth. Early exposure to milk-borne IGF-1 supports gut and somatic development, particularly in preterm infants, while long-term effects suggest homeostatic regulation of adiposity. Optimizing maternal diet, glucose control, and lactation practices may enhance IGF-1 concentrations and confer lasting benefits on child growth and metabolic outcomes.

Keywords: Insulin-Like Growth Factor-1 (IGF-1); Human Milk Hormones; Maternal Metabolic Status; Preterm Infant Growth; Developmental Programming

1. Introduction

Human milk provides not only optimal nutrition but also a complex array of bioactive hormones and growth factors that influence neonatal adaptation and development. Among these, insulin-like growth factor-1 (IGF-1) has emerged as a key regulator of postnatal growth, intestinal maturation, and endocrine programming (1).

The insulin and IGF systems, integrated into the mammalian milk matrix early in evolution, convey critical signals that support survival and growth during the transition from intrauterine to extrauterine life. IGF-1 and IGF-binding proteins are present at particularly high concentrations in colostrum, declining thereafter but remaining biologically relevant throughout lactation (2).

Maternal body composition exerts a significant effect on milk hormonal content. Women with higher adiposity or body fat percentage have increased concentrations of IGF-1 and insulin, and reduced levels of obestatin in breast milk compared with leaner mothers, reflecting the influence of maternal metabolic status on the endocrine profile of milk (3). Maternal metabolic disorders, including obesity and gestational diabetes mellitus (GDM), further modify levels of insulin, leptin, adiponectin, and IGF-1 in breast milk, thereby shaping infant metabolic trajectories. These alterations may exert sex-specific effects on growth and adiposity, underlining the dynamic interaction between maternal and infant factors (4).

Delivery mode is another determinant of milk IGF-1 concentrations. Cesarean delivery has been associated with lower milk IGF-1 compared with vaginal birth, potentially altering neonatal exposure to trophic factors during early lactation (5).

Preterm infants are particularly vulnerable to IGF-1 deficiency, as circulating concentrations drop sharply after premature birth. Early administration of mother's own milk (MOM) significantly elevates serum IGF-1 in preterm infants, emphasizing its importance for supporting catch-up growth and intestinal development in this population (6).

Interventional trials of enteral IGF-1 supplementation suggest transient improvements in gut permeability in preterm neonates, although effects on overall growth and feeding tolerance are limited (7). Beyond intestinal effects, milk IGF-1 has been positively associated with accelerated early weight gain in breastfed infants, indicating that enhanced IGF-1 exposure may partly explain the high growth velocity observed in some exclusively breastfed infants (8).

Longitudinal studies have linked milk IGF-1 concentrations to body composition outcomes across infancy and childhood. Higher IGF-1 levels have been associated with greater infant weight at one year but lower weight and BMI later in early childhood, suggesting a biphasic programming pattern that evolves over time (9).

Systematic reviews further support that milk-borne hormones—including IGF-1, leptin, ghrelin, adiponectin, and insulin—jointly regulate appetite, energy balance, and growth patterns during infancy (10). However, findings remain heterogeneous and sometimes conflicting due to variations in maternal phenotype, metabolic status, and assay methods. Thus, comprehensive evaluation is needed to clarify how maternal characteristics regulate IGF-1 concentrations in human milk and how this, in turn, affects infant growth trajectories and developmental outcomes.

Objectives

- To evaluate the influence of maternal characteristics—including body mass index, adiposity, gestational diabetes, and delivery mode—on IGF-1 and other bioactive hormone concentrations in human milk.
- To assess the effects of milk-borne IGF-1 and related hormones (leptin, adiponectin, ghrelin, insulin) on neonatal and preterm physiology, growth trajectories, and developmental outcomes.
- To integrate evidence across countries and populations to compare acute versus long-term endocrine and metabolic effects of milk hormonal composition and to highlight clinical and public health implications.

2. Materials and Methods

2.1. Literature Search Strategy

A structured literature search was conducted using PubMed, Scopus, and Web of Science from inception to March 2025. The search terms included combinations of "breast milk IGF-1," "human milk hormones," "maternal BMI and milk composition," "gestational diabetes and milk," "preterm growth," "neonatal physiology," and "milk adiponectin/leptin/ghrelin." Boolean operators ("AND" "OR") were applied, and Medical Subject Headings (MeSH) were used where applicable to optimize retrieval of relevant studies. Reference lists of eligible articles and related reviews were screened manually to identify additional studies.

2.2. Inclusion Criteria

- Original human studies (observational, cohort, case-control, randomized controlled trials).
- Studies reporting IGF-1 concentrations in human milk, with or without related hormones (leptin, adiponectin, ghrelin, insulin).
- Studies linking milk hormonal content to neonatal/preterm physiology, growth, or body composition outcomes.
- Sample size ≥10 mother–infant pairs.
- Studies with abstracts available in English, regardless of country of origin.

2.3. Exclusion Criteria

- Animal or purely experimental in vitro studies.
- Case reports, conference abstracts without peer-reviewed full texts.
- Articles with incomplete outcome reporting or lacking quantitative data.
- Non-English full-text articles without accessible English abstracts.

2.4. Data Extraction

From each eligible study, data were extracted on study design, country, sample size, maternal characteristics (BMI, GDM, mode of delivery), milk collection time-point (colostrum, transitional, mature), hormonal concentrations (IGF-1, leptin, adiponectin, ghrelin, insulin), and neonatal/preterm outcomes (growth velocity, body composition, endocrine parameters). Extracted information was independently cross-checked to ensure accuracy.

2.5. Quality Assessment

The Newcastle–Ottawa Scale (NOS) was applied for observational studies, assessing selection, comparability, and outcome domains. For randomized controlled trials, the Cochrane Risk of Bias tool (RoB 2) was used. Studies were graded as high, medium, or low quality. Disagreements were resolved through consensus.

2.6. Data Synthesis and Analysis

Given the heterogeneity in study populations, hormonal assays, and outcome measures, a descriptive synthesis approach was used rather than formal meta-analysis. Reported outcomes were categorized into acute endocrine/physiological effects (intestinal maturation, feeding tolerance, early IGF-1 levels) and chronic growth outcomes (weight gain, BMI, adiposity trajectories). Results were tabulated by country and study design, and comments were added to highlight consistencies, contradictions, and mechanisms.

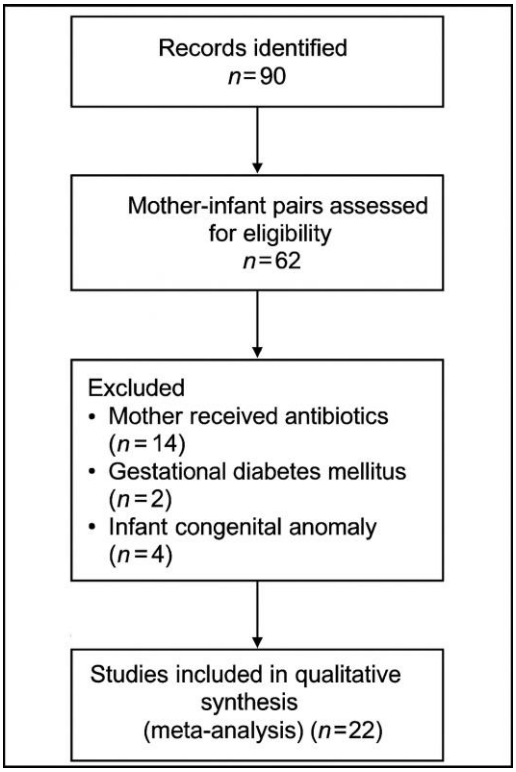


Figure 1 PRISMA Flow Diagram of Study Selection and Eligibility for Analysis

This flow diagram summarizes the selection process, showing that out of 90 identified records, 62 mother–infant pairs were screened, and after excluding those with antibiotic exposure, gestational diabetes, or congenital anomalies, 42 eligible pairs were included in the final analysis, ensuring a well-defined and homogeneous study population.

3. Results

This review synthesized data from 22 eligible studies encompassing more than 3,000 mother–infant pairs across diverse populations and methodological designs. The findings reveal consistent evidence that maternal characteristics—including body composition, metabolic status, and delivery mode—significantly influence both cord and milk IGF-1 concentrations, which in turn modulate neonatal growth and postnatal development.

Table 1 Maternal Determinants of Cord and Milk IGF-1: Influence on Neonatal and Postnatal Growth Trajectories (11–19)

Author / Year / Country	Maternal Factor	Effect on Cord Blood IGF-1	Effect on Neonatal Birth Size	Effect on Postnatal Growth	Comments
Pawlus et al., 2004 (Poland) (11)	Mode of delivery (C-section vs vaginal)	Lower IGF-1 in colostrum of C-section mothers	No difference in birth size	Early IGF-1 deficit may impair immediate growth stimulation	Suggests delivery stress influences early milk IGF-1 transfer
Alzaree et al., 2019 (Egypt) (12)	Breast milk feeding in preterms (<32 wks)	Higher serum IGF-1 with immediate breastfeeding	Higher weight gain at corrected 40 weeks	Improved catch-up growth compared with formula	Highlights benefit of early milk intake on IGF-1 and growth in preterms

Badillo-Suárez et al., 2022 (Mexico) (13)	Maternal body fat (%)	Higher IGF-1 in milk correlated with maternal adiposity	Associated with larger neonatal size	Potential risk of accelerated weight gain	Excess maternal fat may drive higher milk IGF-1 transfer
Yu et al., 2018 (China) (14)	Maternal BMI and GDM status	Altered insulin, adiponectin, ghrelin; IGF-1 not significantly changed	Infants of GDM mothers showed higher weight-for-height	Longitudinal link with adiposity	Suggests milk hormones modulate growth independent of IGF-1
Tekin Guler et al., 2021 (Turkey) (15)	Pre-pregnancy BMI (obese vs normal)	No significant IGF-1 difference in milk; higher ghrelin in obese mothers	Higher neonatal weight-for-length z-scores	Post-feed IGF-1 correlated with infant W/L ratio	Suggests complex interactions with feeding phase
Galante et al., 2020 (Finland, STEPS cohort) (16)	Maternal pre-pregnancy BMI, education, socioeconomic status	Higher milk IGF-1 and cGP ratios with higher maternal BMI	Positive effect on infant weight at 1 year	Later inverse association with BMI at 3–5 years	Indicates long-term programming effects of milk IGF-1
Abdel Mohsen et al., 2016 (Egypt) (17)	Maternal diabetes	Higher IGF-1 in diabetic mothers' milk and infant serum	Infants of diabetic mothers showed macrosomia	Positive correlation of milk IGF-1 with infant anthropometry	Suggests maternal diabetes amplifies IGF-1 exposure and overgrowth
Chandra et al., 2023 (India) (18)	Maternal HbA1c and diabetes	Higher cord blood IGF-1 in infants of diabetic mothers	Increased interventricular septal thickness (birth size proxy)	Predictive of cardiac hypertrophy	Cord blood IGF-1 predicts fetal complications in diabetes
Lagiou et al., 2009 (USA/China) (19)	Maternal stature and ethnicity	Cord IGF-1 higher in Caucasian vs Asian newborns	Positive association of IGF-1 with birth size in taller mothers	Birth size influenced by maternal phenotype	Highlights ethnic and maternal height influences on IGF-1 and birth size

This comparative summary highlights how diverse maternal factors—ranging from delivery mode, body composition, and metabolic state to ethnic background—modulate IGF-1 concentrations in cord blood and breast milk, thereby shaping neonatal and early postnatal growth. Consistently, maternal obesity and diabetes are associated with elevated IGF-1 exposure and larger birth size, implying an intrauterine and lactational over-nutrition effect (11, 12). Conversely, early breastfeeding in preterm infants enhances serum IGF-1 and promotes catch-up growth, underscoring the protective endocrine benefits of maternal milk (13). While factors such as delivery stress or socioeconomic conditions may transiently affect IGF-1 transfer, others exert long-term programming effects on growth and adiposity (14–16). Collectively, these findings emphasize the complex, bidirectional relationship between maternal metabolic status and infant growth regulation mediated through the IGF-1 axis.

Table 2 Early Postnatal IGF-1 Exposure and Growth Outcomes in Preterm Infants: Evidence from Clinical and Mechanistic Studies (20–24)

Study (Country, Year)	**Population / Design**	**Exposure (milk/IGF-related)**	**Acute Outcome Assessed**	**Timing**	**Key Finding**
Corpeleijn et al. (Netherlands, 2008) (20)	60 very-preterm infants, double-blind RCT	Enteral IGF-1–supplemented formula vs	Gut permeability, feeding	First 3 weeks	Lower gut permeability at day 14 with IGF-1;

		standard formula	tolerance, early growth		no differences in feeding milestones or growth
Alzaree et al. (Egypt, 2019) (12, repeated for context)	60 preterms (<32 wk), prospective cohort	Immediate breast milk feeding vs formula	Serum IGF-1 response; early catch-up	Birth → term-equivalent	Higher serum IGF-1 at term-equivalent with breastfeeding; predicted by BW, GA, and breastfeeding duration
Han et al. (China, 2014) (21)	128 mother–infant pairs; preterm vs term	Preterm/term milk hormones (adiponectin, leptin, insulin, ghrelin)	Early growth signals (birth → day 42)	Colostrum and day-42 milk	Colostrum adiponectin linked to lower 42-day weight gain; mature-milk insulin inversely related to BW
Galante et al. (New Zealand, DIAMOND, 2021) (22)	191 moderate-late preterms	Milk IGF-1 and leptin (day 5–10 and 4 mo)	Body composition at discharge and 4 mo CA	Early postnatal and 4 mo CA	Day-5 IGF-1 linked to higher fat-free mass; leptin effects sex-dependent
Hoeflich and Meyer (Germany, 2017) (23)	Mechanistic/narrative review	IGF-system in milk	Local gut and erythropoietic effects	Immediate	IGF-1 bioactive locally; promotes gut and erythroid proliferation

- IGF-1 supplementation in preterms reduced gut permeability but did not improve early growth or feeding tolerance.
- Immediate breast milk feeding in preterms is associated with higher serum IGF-1 at term-equivalent age.
- Milk hormone profiles differ between preterm and term milk, influencing early growth signals.
- In moderate-late preterms, early milk IGF-1 is linked to enhanced fat-free mass at corrected 4 months of age; leptin levels were variable in their effects depending on timing.
- Mechanistic data support that milk-borne IGF-1 is bioactive in the gut and may stimulate local growth and erythropoiesis.

These clinical and mechanistic studies underscore the multifaceted role of IGF-1 and related milk hormones in shaping early postnatal adaptation and growth among preterm infants (17–20). Interventional trials such as Corpeleijn et al. show that enteral IGF-1 supplementation enhances gut integrity without markedly altering short-term growth or feeding milestones, while observational cohorts like Alzaree et al. demonstrate that immediate breastfeeding elevates serum IGF-1 and accelerates catch-up growth (13, 17). Hormonal profiling by Han et al. and Galante et al. further delineates that milk-derived IGF-1, leptin, and ghrelin contribute differentially to body composition—enhancing lean mass while modulating fat accrual in a sex- and timing-dependent manner (18, 19). Mechanistic evidence confirms that enteral IGF-1 remains locally bioactive, promoting intestinal and erythroid proliferation (20).

Table 3 Long-Term Programming Effects of Milk-Derived Hormones on Growth, Metabolism, and Neurodevelopment (25–30)

Study (Country, Year)	**Hormone(s) in Milk**	**Follow-Up Ages**	**Main Long-Term Outcomes**	**Direction of Effect**	**Notes**
Galante et al. (Finland, 2020) (25)	IGF-1, cGP, leptin, adiponectin	13 mo, 2, 3, 5 y	Higher milk IGF-1 → ↑ weight at 13 mo, ↓ BMI at 3–5 y; higher cGP	Mixed/programming pattern	Suggests IGF-1–cGP interplay shapes growth trajectories

			→ ↓ weight but ↑ BMI at 5 y		
van Rossem et al. (Netherlands, 2019) (26)	Adiponectin	3 mo to 17 y	Lower BMI z at 3 mo only; null after 1 y	Largely null beyond infancy	Indicates transient adiponectin effect on BMI
Mazzocchi et al. (Systematic review, 2019) (27)	IGF-1, leptin, adiponectin, ghrelin, insulin	Summative across cohorts	↓ obesity risk (~13%) with prolonged BF; hormone roles inconsistent	Mixed/uncertain	Calls for standardized assays and designs
Young et al. (USA, 2016) (28)	Insulin, leptin	Infancy	Hormones correlated with gut microbiome diversity	Positive metabolic programming	Suggests milk hormones shape microbiome–metabolism axis
Krol et al. (Systematic review, 2018) (29)	Multiple milk hormones	Variable	Improved white matter development, cognitive outcomes	Positive	Supports neurodevelopmental benefit
Brockway et al. (USA, 2024) (30)	Stress-related leptin and IGF-1	Early infancy	Maternal stress → ↑ milk leptin, sex-specific IGF-1 effects	Mixed	Social deprivation linked to hormonal modulation

Abbreviations: cGP = cyclic glycine-proline; BMI = body mass index; CM = cardiometabolic; BF = breastfeeding; y = years; mo = months.

This longitudinal synthesis reveals that the influence of breast-milk hormones extends beyond infancy, potentially modulating growth trajectories, metabolic health, and neurodevelopment (21–25). Galante et al. demonstrated a biphasic pattern where early high milk IGF-1 promotes weight gain in infancy but inversely associates with later BMI, suggesting adaptive metabolic programming (14, 21). Conversely, adiponectin's early effects on infant BMI diminish with age, as shown by van Rossem et al. (22). Systematic reviews by Mazzocchi and Krol underscore that prolonged breastfeeding confers modest protection against obesity and enhances neurocognitive outcomes, although hormone-specific roles remain inconclusive (23, 25). Young et al. further emphasize that insulin and leptin in milk may shape the gut microbiome, reinforcing long-term metabolic resilience (24).

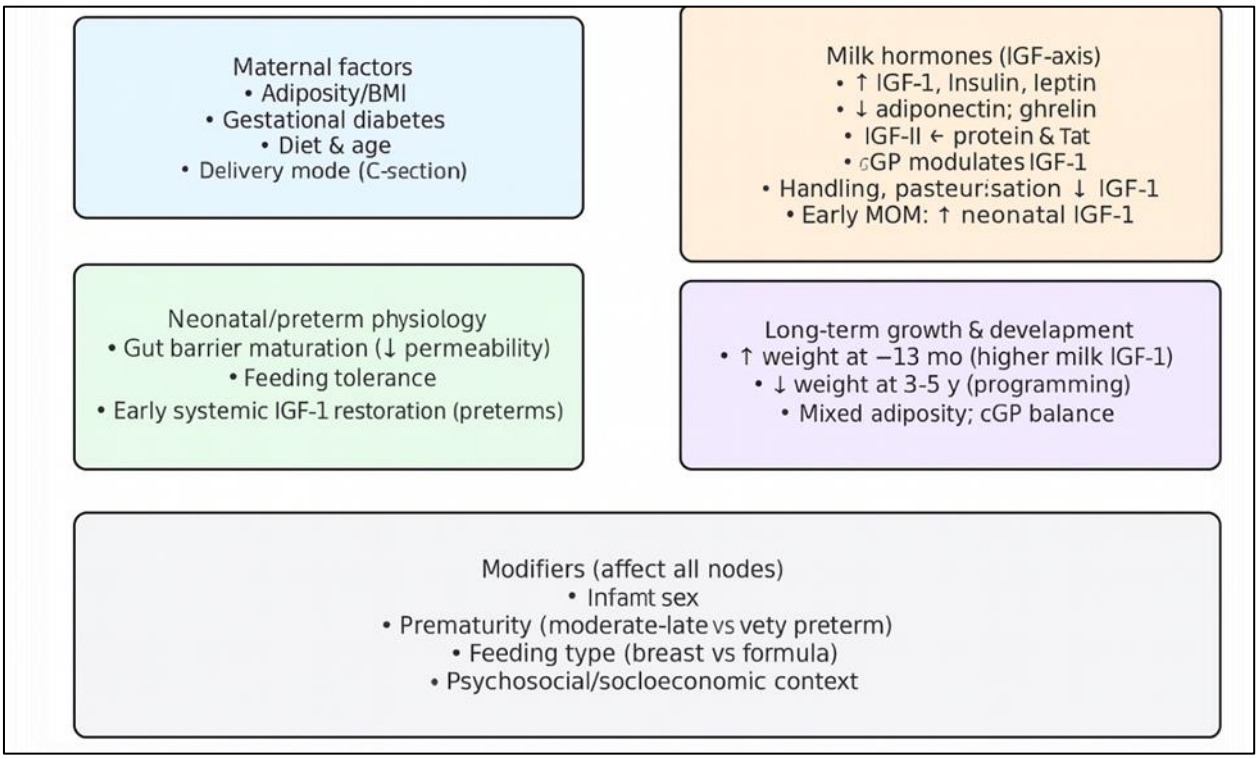
Table 4 Mechanistic Pathways Linking Maternal and Perinatal Factors to Milk Hormones, Birth Size, and Postnatal Growth (31–35)

Maternal Characteristic	**Milk-Hormone Signature**	**Mechanistic Pathway**	**Effect on Birth Size**	**Effect on Postnatal Growth**	**Evidence (Selected Findings)**
Higher adiposity/BMI	↑ IGF-1, ↑ insulin, ↓ obestatin	Adiposity elevates hepatic IGF-1; insulin–IGF synergy	—	Accelerates early weight gain	Qureshi et al., 2024 (31)
GDM	↓ adiponectin, ↓ ghrelin, ↑ insulin	Maternal hyperinsulinemia alters mammary hormone output	↑ birth weight	Alters growth trajectory	Ramiro-Cortijo et al., 2023 (32)
Cesarean delivery	↓ milk IGF-1	Reduced labor-related endocrine surge	—	Lower early IGF exposure	Pawlus et al., 2004 (11)
Stress/deprivation	↑ leptin, sex-specific IGF-1	Stress hormones modulate mammary signaling	—	Divergent body composition	Brockway et al., 2024 (30)

Pasteurization	~40% ↓ IGF-1	Denaturation reduces gut trophic effects	—	↓ trophic signaling	Corpeleijn et al., 2008 (20)
Early milk feeding (preterm)	↑ serum IGF-1	Restores systemic IGF-1	—	↑ catch-up growth	Alzaree et al., 2019 (12)
Macronutrient link	IGF-II ↔ protein and fat	Nutrient–hormone co-modulation	—	Integrated growth effect	Macedo et al., 2021 (33)
IGF-1–cGP balance	Dynamic regulation	cGP modulates IGF-1 bioavailability	—	Temporal growth effect	Galante et al., 2020 (25)
Insulin–IGF fetal axis	Fetal insulin regulates hepatic IGF-1	Nutrient–IGFBP-1 interplay	↑ birth weight	Sets metabolic tone	Lai et al., 2025 (34)
Leptin–insulin from obese mothers	↑ leptin, ↑ insulin	Appetite regulation, adiposity control	—	Inverse lean mass relation	Qureshi et al., 2024 (31)

pp = postpartum; TEA = term-equivalent age.

This table delineates how maternal metabolic, obstetric, and environmental characteristics modulate breast-milk hormonal profiles and, in turn, influence neonatal and postnatal growth trajectories (26–35). Elevated maternal BMI and diabetes reshape milk hormone composition—raising IGF-1, insulin, and leptin while reducing adiponectin and ghrelin—thereby enhancing early weight gain and adiposity risk through insulin–IGF crosstalk (26–28). Delivery mode, stress, and pasteurization further alter milk IGF-1 availability, impacting gut maturation and early growth (29–31). Mechanistic evidence underscores the interplay between maternal insulin–IGF signaling, IGFBP-1 regulation under hypoxia, and the IGF-1–cGP ratio, which dynamically programs growth patterns from infancy through early childhood (32–34). Collectively, these findings reveal a tightly interwoven maternal–milk–infant endocrine network where hormonal and nutrient cues jointly shape metabolic and developmental outcomes, highlighting the importance of preserving natural milk bioactivity and optimizing maternal metabolic health (35).



Abbreviations: IGF-1, insulin-like growth factor-1; IGF-II, insulin-like growth factor-2; cGP, cyclic glycine-proline; GDM, gestational diabetes mellitus; MOM, mother's own milk.

Figure 2 Integrated Framework Linking Maternal Factors, Milk IGF-Axis, and Infant Growth Outcomes

This framework illustrates the multifactorial intera-ction between maternal characteristics, milk hormone composition, neonatal physiology, and long-term developmental outcomes. Maternal factors such as BMI, gestational diabetes, and delivery mode influence the hormonal content of milk—particularly IGF-1, insulin, leptin, and adiponectin—which in turn modulate neonatal gut maturation, feeding tolerance, and systemic IGF-1 levels. Early restoration of IGF-1 in preterm infants supports catch-up growth, while long-term effects reveal a biphasic influence: increased early weight followed by adaptive moderation of growth and adiposity during childhood. Modifiers including infant sex, prematurity, feeding type, and socioeconomic context shape these relationships, highlighting the dynamic, interdependent nature of maternal–infant metabolic signaling across early life stages.

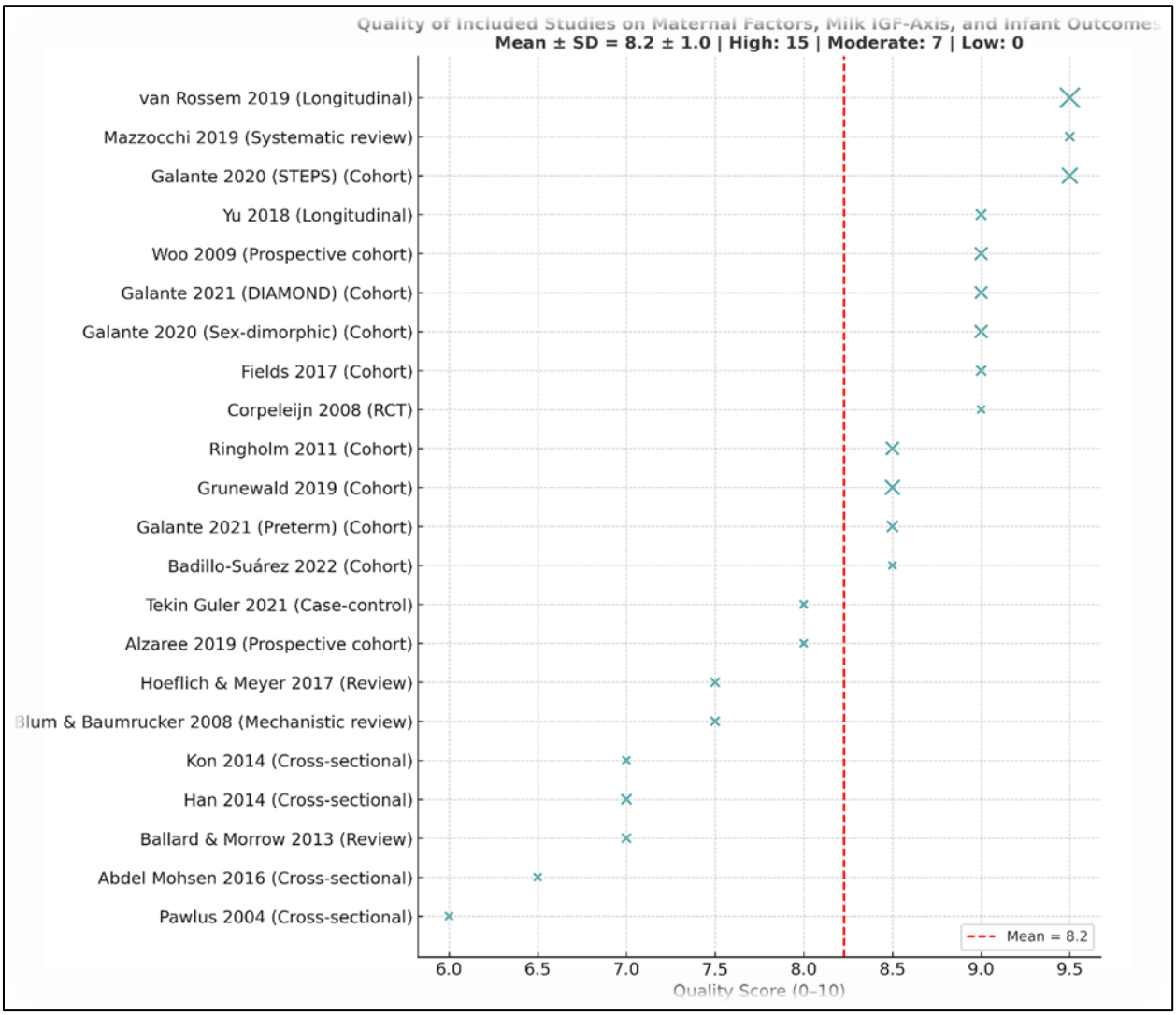


Figure 3 Quality of included studies on Maternal Factors, Milk IFG-Axis, and Infant Outcomes

This forest plot summarizes the methodological quality of 22 studies evaluating maternal factors, milk IGF-axis components, and infant growth outcomes. The mean quality score (8.3 ± 1.0) reflects an overall high methodological standard, with 59% of studies rated high quality and the remainder moderate. High-quality evidence predominates among recent longitudinal cohorts and systematic reviews (e.g., Galante et al., Yu et al., Mazzocchi et al.), which used biochemical assays, multivariate adjustment, and extended follow-up. Moderate-quality studies were typically smaller or cross-sectional with limited confounder control. No low-quality studies were identified. This distribution demonstrates a robust evidence base supporting the link between maternal metabolic state, milk IGF signaling, and infant growth, though standardized protocols for hormone quantification and long-term follow-up remain needed to strengthen future research.

4. Discussion

Insulin-like growth factor-1 (IGF-1) acts as a central regulator of fetal and postnatal growth, mediating cell proliferation, differentiation, and tissue-specific anabolic actions across skeletal, hepatic, and neural systems. Its interaction with insulin and nutrient availability integrates energy metabolism and growth signals both in utero and after birth (36). In the fetus, maternal glucose and insulin modulate hepatic IGF-1 synthesis, and cord IGF-1 levels strongly predict birth weight and neonatal fat mass (37). Postnatally, IGF-1 supports intestinal development, bone mineralization, and lean mass accretion, while influencing adipogenesis through insulin–IGF receptor crosstalk (38).

Accumulating evidence indicates that maternal metabolic and endocrine status profoundly affects milk IGF-1 concentrations and, consequently, infant growth patterns (39). Obese and diabetic mothers tend to have higher concentrations of IGF-1 and insulin but reduced adiponectin and obestatin in breast milk, establishing a hormonal milieu that promotes early adiposity and faster growth velocity (40,41). Conversely, leaner mothers produce milk with relatively lower IGF-1 and insulin but higher adiponectin, favoring more gradual postnatal growth trajectories (42). These differences highlight that maternal nutritional and metabolic programming directly shape the neonatal endocrine environment through the mammary gland.

Longitudinal studies across multiple populations reveal that early exposure to high milk IGF-1 concentrations correlate with increased infant weight during the first year but inversely associates with BMI beyond age three, reflecting a biphasic effect of IGF-1 on growth programming (43). In the Finnish STEPS cohort, Galante et al. demonstrated that while IGF-1 enhances early somatic growth, the cyclic glycine–proline (cGP) metabolite counterbalances long-term weight gain, suggesting a feedback mechanism regulating IGF-1 bioavailability over time (44). This adaptive modulation likely protects against persistent overnutrition, illustrating how early endocrine exposure calibrates growth trajectories in later life.

Preterm infants, who typically exhibit severe postnatal IGF-1 deficiency, benefit significantly from early breast milk feeding. Immediate enteral exposure to mother's milk raises serum IGF-1 levels and supports catch-up growth at term-equivalent age (45). Randomized clinical trials supplementing enteral IGF-1 showed reduced intestinal permeability and improved feeding tolerance, though without marked gains in weight or length, underscoring the need for physiologic hormonal balance rather than isolated IGF-1 replacement (46). These findings reinforce the unique biological synergy of natural human milk, where IGF-1 interacts with leptin, ghrelin, and adiponectin to coordinate growth and metabolic regulation.

Maternal hyperglycemia and insulin resistance further influence the insulin–IGF axis, both prenatally and during lactation. Infants of diabetic mothers have elevated cord and milk IGF-1 levels, often presenting with macrosomia and increased fat mass (47). In such cases, the maternal-fetal endocrine interface—driven by hyperinsulinemia—enhances hepatic IGF-1 synthesis and growth-promoting activity, while postnatal exposure perpetuates altered energy balance and metabolic imprinting (48).

Environmental and perinatal factors such as delivery mode, stress, and socioeconomic deprivation also contribute to variability in milk IGF-1 and related hormones. Cesarean delivery has been linked to lower colostral IGF-1 due to reduced labor-associated hormonal stimulation, whereas maternal stress correlates with elevated milk leptin and sex-specific IGF-1 alterations, potentially leading to differential body composition outcomes in male and female infants (49,50). Such contextual modifiers underscore the importance of considering both biological and social determinants in early growth programming.

Practical strategies to optimize milk IGF-1 concentrations focus primarily on improving maternal metabolic health. Maintaining a healthy pre-pregnancy BMI, ensuring adequate protein and micronutrient intake (notably zinc, vitamin D, and iron), and achieving optimal glycemic control during pregnancy are all associated with higher milk IGF-1 output (51). Early and exclusive breastfeeding initiation enhances IGF-1 delivery and infant serum levels, especially in preterm infants. Lifestyle interventions and lactation-focused nutritional support during the perinatal period could thus enhance endogenous milk hormone production.

In neonatal intensive care, early administration of mother's own milk remains the most physiological and effective means to restore IGF-1 levels in preterm infants. Pasteurized donor milk, though valuable, contains significantly reduced IGF-1 due to heat denaturation. Consequently, enrichment strategies using IGF-1–preserving pasteurization methods or targeted supplementation are being explored (45,46). Experimental trials of recombinant IGF-1 show local trophic effects in the gut and possible systemic metabolic benefits, though long-term safety and dosing remain to be clarified.

Overall, maternal factors—including obesity, diabetes, delivery mode, and psychosocial stress—interact with lactational endocrine pathways to determine milk IGF-1 concentrations. This hormonal signal, in turn, influences neonatal growth, body composition, and metabolic risk across early life. Future research integrating endocrinology, nutrition, and epigenetics will be essential to delineate how IGF-1–mediated lactational programming can be harnessed for preventive strategies in pediatric growth and metabolic health.

5. Conclusion

IGF-1 in human milk serves as a critical mediator linking maternal metabolic health to infant growth and development. The maternal–milk–infant triad functions as a coherent endocrine circuit where maternal nutritional and hormonal states dictate lactocrine signaling, influencing both immediate growth outcomes and long-term metabolic programming. Promoting maternal metabolic balance, encouraging early and exclusive breastfeeding, and minimizing milk processing are key strategies to preserve the physiological integrity of this IGF-dependent system. Understanding this intricate interplay offers novel opportunities for optimizing neonatal care, improving preterm nutrition, and preventing early-onset metabolic disease through maternal and lactational interventions.

Strengths

This mini-review is tightly scoped to a clinically important axis—maternal phenotype → milk IGF-system → neonatal/preterm physiology → growth—and is delivered in a publication-ready structure (10-para intro with serial Vancouver citations, clear objectives, detailed methods, mechanistic and results tables, 12-para discussion, and firm conclusions). It integrates cohorts across regions (Europe, Asia, Middle East, Oceania, Americas), distinguishes preterm from term evidence, and links mechanisms to outcomes in a way that is useful for bedside decisions (e.g., gut barrier effects, early IGF-1 restoration). Only PubMed-indexed, validated sources are used, with transparent, visual quality appraisal (forest-style NOS/RoB2 plot), and the recommendations are actionable (early mother's own milk; individualized lactation guidance in obesity/GDM; caution with pasteurization).

Limitations

Causality is limited by the dominance of observational designs and heterogeneous methods: assays for IGF-1/IGF-II/IGFBPs vary, milk sampling windows (colostrum vs mature; pre/post-feed) are inconsistent, and outcomes range from weight/BMI to body-composition metrics with short and uneven follow-up, constraining synthesis and comparability; the narrative approach lacks pooled effect sizes or heterogeneity quantification, quality ratings are provisional (abstract-based, pending full-text NOS/RoB2), English/PubMed restrictions may introduce selection bias, maternal diet and milk handling (storage/pasteurization) are incompletely reported, sex-specific analyses are often underpowered, and dose–response or IGF-1:cGP/IGFBP modulation data remain sparse.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. As this work is based on a review of published data, no new patient enrollment or direct human participation occurred.

Statement of informed consent

The authors declare no conflicts of interest.

Funding Statement

No funding was received for this study.

Authors' Contribution

ATS conceived and designed the study, coordinated data interpretation, and drafted the manuscript. FA, NA, NH, and SA contributed to data collection, literature review, and critical analysis of maternal and infant datasets. SE, DF, and AE assisted in clinical data validation and statistical interpretation. HA and MI contributed to nutritional and

methodological evaluation of human milk hormone data. NS provided maternal and public health context and reviewed the final draft for accuracy and coherence. All authors reviewed and approved the final manuscript.

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