Rocz Panstw Zakl Hig 2025;76(3):259-271
https://roczniki.pzh.gov.pl/
https://doi.org/10.32394/rpzh/217603

ORIGINAL ARTICLE

LONGITUDINAL GROWTH TRAJECTORIES OF PRETERM INFANTS WITH AND WITHOUT INTRAUTERINE GROWTH RESTRICTION UP TO 24 MONTHS OF CORRECTED AGE: THE INFLUENCE OF EARLY FEEDING PATTERNS

Nouhayla Bouali[1,2], *Khalid El Kari*[3], *Fatima Zahra Laamiri*[4], *Ilham Elouardighi*[5], *Lamyae Elyazigi*[5], *Imane Zizi*[5], *Redouane Belouali*[1], *Hassan Aguenaou*[3], *Amina Barkat*[5] and *Mohamed Khalis*[1,2]

[1]Public Health, Mohammed VI International School of Public Health, Mohammed VI University of Sciences and Health, Casablanca, Morocco
[2]Public Health, Department of Public Health and Clinical Research, Mohammed VI Center for Research and Innovation, Rabat, Morocco
[3]Joint Research Unit on Nutrition and Food, RDC-Nutrition AFRA/IAEA, Ibn Tofail University-CNESTEN, Rabat-Kénitra, Morocco
[4]Hassan First University of Settat, Higher Institute of Health Sciences, Laboratory of Health Sciences and Technologies, Settat, Morocco
[5]Research Team on Maternal and Child Health and Nutrition, Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco

ABSTRACT

Background. Intrauterine growth restriction (IUGR) is common in premature infants and can significantly impact long-term physical and neurological development. While breastfeeding is the gold standard for nutrition, its role in optimizing postnatal growth for this specific population requires further investigation.

Objective. This study compared growth trajectories specifically weight, length, and head circumference between preterm infants with and without IUGR at 1, 3, 6, 12, and 24 months of corrected age (CA) in Rabat. It also evaluated the impact of maternal feeding during the first six months (CA).

Methods. This prospective study, conducted at the National Reference Center for Neonatology and Nutrition, followed 45 breastfed preterm infants (25 with IUGR; 20 without). Anthropometric data were collected over two years and compared against WHO growth standards and Fenton curves.

Results. Infants with IUGR had significantly lower birth weights and maintained lower weight throughout the follow-up ($p < 0.05$). At discharge, extrauterine growth restriction (EUGR) was present in 100% of the IUGR group and 80% of the without-IUGR group. By 3 months (CA), EUGR incidence decreased but remained length in the IUGR group (32% vs. 10%). Stunting was consistently more prevalent in IUGR infants: 92% vs. 75% at 1 month (CA), 64% vs. 25% at 3 months (CA), 24% vs. 0% at 6 months (CA), and 12% vs. 0% at 12 months (CA). By 24 months (CA), both groups reached normal weight, length, and head circumference. Notably, the feeding type showed no significant effect on growth parameters at 3 or 6 months (CA) ($p > 0.05$).

Conclusion. IUGR preterm infants exhibit significantly poorer growth than their without-IUGR peers. Although maternal feeding offers essential benefits, it does not fully prevent growth restriction. Continuous monitoring and individualized nutritional management are crucial to optimize long-term outcomes.

Keywords: *anthropometry, breastfeeding, prematurity, low birth weight, growth retardation*

INTRODUCTION

The survival of preterm infants has improved significantly over the last decade due to major advancements in perinatal medicine and neonatology [1]. However, this increased survival is paradoxically accompanied by a high burden of long-term morbidity, which remains closely proportional to the degree of

Corresponding author: Nouhayla Bouali, Public Health, Mohammed VI International School of Public Health, Mohammed VI University of Sciences and Health, Casablanca, Morocco; phone: 00212611512063; email: nbouali@um6ss.ma
Senior authorship: Amina Barkat and Mohamed Khalis contributed equally to the supervision of this paper

Publisher: National Institute of Public Health NIH - National Research Institute

prematurity [2]. Among the myriad of challenges faced by these vulnerable neonates, achieving optimal postnatal growth remains a primary concern. Growth failure in this population is often rooted in complex maternal-fetal complications, such as preeclampsia or placental insufficiency, which frequently necessitate early medical induction or cesarean section [1, 3].

Intrauterine growth restriction (IUGR) represents a critical clinical entity that significantly compounds the vulnerability of preterm infants. Beyond the immediate risk of neonatal mortality, IUGR is associated with specific systemic complications, including patent ductus arteriosus and impaired metabolic programming [4]. Characterized by a birth weight below the 10th percentile, IUGR reflects a failure to achieve genetic growth potential in utero, leaving the infant with limited nutritional reserves [5]. This initial deficit is frequently exacerbated during the hospital stay by extrauterine growth restriction (EUGR), a condition where the infant fails to maintain the expected growth velocity after birth [6, 7].

Global epidemiological data underscore the magnitude of this challenge. The prevalence of EUGR shows significant geographic and clinical variability, reaching 43.5% in China [8], 47% in Indonesia [9], and 46% in India [10]. Notably, in extremely preterm cohorts, such as those studied in Turkey, the prevalence can soar to 74%, highlighting the critical need for standardized nutritional strategies [11].

To mitigate these risks, precise anthropometric monitoring is essential. This requires a sophisticated transition between monitoring tools: the Fenton 2013 or INTERGROWTH-21st curves are utilized to assess growth during the intensive care period [5, 6], while the World Health Organization (WHO) standards are adopted after 50-52 weeks of postmenstrual age to ensure continuity and international comparability of long-term trajectories [6].

Despite the availability of these standardized tools, there remains a significant research gap regarding the 24-month longitudinal trajectories of IUGR infants in North African populations. Specifically, the interplay between early nutritional interventions particularly the role of breastfeeding in promoting healthy catch-up growth while avoiding metabolic over-nutrition, remains insufficiently characterized. This study aims to compare the growth trajectories including weight, length, and head circumference between preterm infants with and without intrauterine growth restriction (IUGR) at 1, 3, 6, 12, and 24 months of corrected age, at the National Reference Center for Neonatology and Nutrition in Rabat. Additionally, the study aimed to evaluate the impact of maternal feeding during the first six months of corrected age (CA).

MATERIALS AND METHODS

Study design and location

We conducted a prospective cohort study of preterm newborns (born at < 37 weeks of gestation) and their mothers, who were admitted to the National Reference Centre for Neonatology and Nutrition, Rabat. From February 2022, data collection continued until November 2024. A total of 45 newborns and their mothers were recruited for the study at birth and followed from hospital discharge to corrected ages of 1, 3, 6, 12, and 24 months. At birth, preterm infants were first classified into two groups via the Fenton 2013 growth charts: those with intrauterine growth restriction and those appropriate for gestational age (AGA) were referred to as those without IUGR in our study. The birth weight of each infant was compared to the corresponding percentile for gestational age: those below the 10th percentile were classified as IUGR, whereas those between the 10th and 90th percentiles were considered without IUGR. The inclusion criteria were as follows: preterm infants born before 37 weeks of gestational age without IUGR; preterm infants born before 37 weeks of gestational age with IUGR, exclusively breastfed at birth; and parental written consent for longitudinal follow-up. The exclusion criteria included major congenital malformations, known genetic syndromes, early neonatal death, loss to follow-up prior to the first corrected visit, and parental refusal.

Study Population

A total of 53 preterm neonates were assessed for eligibility. Eight infants were excluded: four infants were lost due to withdrawal of consent and four infants died. The final cohort comprised 45 preterm infants (25 with IUGR and 20 without IUGR).

Definitions

- Prematurity: Premature birth is defined as birth before the completion of 37 weeks of gestation. It is classified as extremely preterm (before 28 weeks), very preterm (between 28 and 31 weeks) or moderate to late preterm (between 32 and 36 weeks). It is associated with an increased risk of neonatal complications and potential long-term effects on growth and neurodevelopment [1].
- Intrauterine growth restriction (IUGR) is a condition in which a fetus does not reach its genetically determined growth potential. This often results in a birth weight below the 10th percentile for gestational age. IUGR is associated with an increased risk of perinatal complications, as well as long-term effects on growth and neurodevelopment [12].

- Extrauterine growth restriction (EUGR) is defined as postnatal growth failure in preterm infants, typically indicated by weight, length or head circumference below the 10th percentile for corrected age. Compared with intrauterine expectations, reflecting inadequate growth after birth is associated with long-term growth and neurodevelopmental risk [13].
- The corrected age (CA) is the age of a preterm infant adjusted for prematurity. It is calculated by subtracting the number of weeks of prematurity from the infant's chronological age. This provides a more accurate assessment of growth and developmental progress, enabling comparison with the standards for full-term infants of the same age [14].
- The Fenton 2013 growth charts provide sex-specific percentiles for weight, length and head circumference in preterm infants aged 22-50 weeks. Charts are widely used to classify infants as SGA (small for gestational age), AGA (appropriate for gestational age), or LGA (large for gestational age), and to assess intrauterine growth at birth [6].
- Exclusive breastfeeding: The infant receives only breast milk. No other liquids or solids are given, not even water, with the exception of oral rehydration solution, or drops/syrups of vitamins, minerals or medicines [15].
- Mixed feeding (partial breastfeeding): The infant receives both breast milk and infant formula or other non-human milks [16].
- Artificial feeding: The infant receives no breast milk and is nourished solely with commercial infant formula [17].
- Maternal feeding: This group included infants receiving human milk, encompassing both exclusive breastfeeding and mixed feeding (breast milk combined with infant formula or water-based liquids). This category was defined by the continued exposure to the biological benefits of maternal milk [18].

Data collection

Data on maternal and neonatal characteristics were collected from medical records. These characteristics included maternal age, parity, consanguinity, pregnancy complications, medical history, number of antenatal consultations, mode of delivery, hormone use, smoking and alcohol consumption during pregnancy, gestational age at birth, infant sex, and Apgar scores at one and five minutes. The age at which enteral feeding commenced was also recorded. The birth weight, length, and head circumference of newborn babies were measured within 24 hours of delivery using standardized techniques.

The newborns were evaluated at 1, 3, 6, 12 and 24 months (CA). Anthropometric indices (weight, length/height, head circumference (HC)) were measured using the same standardized procedures at each visit. The corrected gestational age was calculated to adjust the growth assessment relative to that of newborns at term. Growth outcomes were assessed using WHO growth charts at each corrected age to identify EUGR.

Nutritional assessment

Infant feeding practices were assessed prospectively at each follow-up visit (1, 3, 6, 12, and 24 months of corrected age) using a structured nutritional questionnaire administered to the mothers. To ensure the depth and accuracy of the nutritional data, mothers were specifically questioned about the introduction of water, other liquids (infusions/teas), and infant formula. This prospective tool allowed us to categorize infants based on their evolving nutritional status: exclusive breastfeeding, partial breastfeeding (mixed feeding), or exclusive formula feeding. The precise duration of exclusive breastfeeding was recorded in months to evaluate its impact as a time-dependent variable.

For the purpose of the comparative analysis during the first semester, feeding status was treated as a longitudinal variable rather than a static baseline. This enabled us to identify the exact weaning point (the transition to 100% artificial feeding) for each infant. At the 3-month and 6-month milestones, infants were categorized into two distinct nutritional cohorts:

Maternal feeding group and artificial feeding group

The duration of any breast milk exposure was recorded in months. For the analysis of growth trajectories up to 24 months, only infants who sustained maternal feeding throughout the critical first 6 months of life were included in the 'breastfed' cohort, ensuring that the results reflect the impact of sustained exposure to human milk versus an exclusively artificial diet.

Anthropometric indices

Anthropometric indices were measured in accordance with the standardized procedures of the World Health Organization (WHO) [19], for assessing the growth of children. Weight, length/height, and HC were measured at birth and at each follow-up appointment at 1, 2, 3, 12 and 24 months (CA). Weight was measured to the nearest 10 grams using a calibrated electronic scale, length to the nearest 0.1 cm using a rigid infant meter, and HC to the nearest 0.1 cm via nonstretchable tape. All indices were measured twice, and the mean value was recorded to ensure accuracy and reproducibility. BMI was calculated as an indicator of body proportions. All anthropometric data were converted into percentiles using WHO growth charts that were appropriate for the infant's age and sex. EUGR was defined as anthropometric indices below the 10th percentile for corrected age. BMI was calculated as an indicator of body proportions. All anthropometric data were converted into percentiles using WHO growth charts that were appropriate for the infant's age and sex. EUGR was assessed in terms of weight-for-age, length-for-age, BMI-for-age, and head circumference-for-age. Infants with a weight below the 15th percentile were considered to have weight-based EUGR; those with a length below the 15th percentile were classified as stunted; infants with low weight-for-length or BMI were considered to have disproportionate growth restriction; and those with an HC below the 15th percentile were classified as having a small head circumference.

Statistical analysis

Statistical analysis and data processing were performed using Excel and R software (version 4.5.1, R Foundation for Statistical Computing, Vienna, Austria). The Kolmogorov-Smirnov test was used to test distribution normality. Categorical variables are expressed as numbers and percentages and were compared using either the *Chi*-square test of independence or Fisher's exact test. Quantitative variables that were normally distributed are expressed as the means and standard deviations and were compared using Student's t-test. Quantitative variables with an abnormal distribution are expressed as the median and quartiles and were compared using the Mann-Whitney test; $p < 0.05$ was considered significant for all the statistical analyses.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2024) and the guidelines of the Council for International Organizations of Medical Sciences (CIOMS, 2016) for research involving human subjects. It also complied with the provisions of Moroccan Law 28-13 on the protection of individuals in biomedical research and Law 09-08 on personal data protection. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine and Pharmacy in Rabat reference number (CERB 13-22). Informed consent to participate in the study was obtained from the parents or legal guardians of all participants under the age of 16, in accordance with ethical guidelines and national regulations.

RESULTS

Maternal and neonatal characteristics

The maternal characteristics are presented in Table 1. The median age of mothers was 27.5 (26-30) years among preterm infants without IUGR, and 34 (29-37) years among preterm infants with IUGR. A significant difference in maternal age was observed between the two groups ($p = 0.033$). Most mothers had no medical history. Hypertension (HTN) was more prevalent among mothers of preterm infants with IUGR than among those without IUGR (20% vs. 5%), although this difference was not statistically significant. Diabetes was more prevalent among mothers of preterm infants without IUGR than among those with IUGR (20% vs. 8%). Among the group with IUGR, 5% did not attend any visits; 10% attended two visits and 85% attended three or more visits. In the group without IUGR, 20% did not attend any visits, 8% attended two visits, and 72% attended three or more visits. There was no significant difference in the distribution of prenatal visits between the IUGR and without-IUGR groups. The majority of deliveries in the without IUGR group were vaginal 75%. Among those in the with-IUGR group, 52% delivered vaginally and 48% delivered by cesarean section. There were no significant differences between the groups in terms of this distribution.

When we analyzed the neonatal data (Table 2), we observed the following distributions by sex: among preterm infants without IUGR, 30% were male and 70% were female. In contrast, among preterm infants with IUGR, 56% were male and 44% were female. The median gestational age for preterm infants without IUGR was 33 (30-36) weeks. For preterm infants with IUGR, the median gestational age was 35 (33-36) weeks. The median length of hospitalization for preterm infants without IUGR was 18 (5-52) days. For those with IUGR, it was 22 (4-54) days. Anthropometric data at birth and discharge for all preterm infants, both with and without IUGR, are presented in Table 2.

Anthropometric indices

At each follow-up visit, the anthropometric indices of preterm infants with IUGR were compared with those of preterm infants without IUGR. Significant differences in weight were observed at 3 months (CA) (4440 (3700-4855) g vs. 4860 (4184-5590) g, $p = 0.048$), 6 months (CA) (6505 (6000-7005) g vs. 7458 (6655-7839) g, $p = 0.0017$), 12 months (CA) (8800 (7860-9500) g vs. 9910 (9223-10803) g, $p < 0.001$) and 24 months (CA) (11000 (10100-13000) g vs. 13000 (12000-15000) g, $p = 0.003$). A significant difference in length was noted at 12 months (CA) (71 (69-72) cm vs. 72 (72-73) cm, $p = 0.004$) and at 24 months (CA) (85 (82-85) cm vs. 85 (84-90) cm, $p = 0.042$). Significant differences in head circumference were observed at 3 months (CA) (38 (36-39.5) cm vs. 38.5 (38-41) cm, $p = 0.045$), 6 months (CA) (42 (41-43) cm vs. 43 (42.8-44) cm, $p = 0.048$), and 12 months (CA)

Table 1. Maternal characteristics

Maternal characteristic	Population N = 45		p-value
	Without IUGR n = 20	With IUGR n = 25	
Age (years), median (25th, 75th percentiles)	27.5 (26-30)[a]	34 (29-37)[a]	0.033[b]
Medical coverage, n (%)			1.000[c]
Yes	18 (90)	23 (92)	
No	2 (10)	2 (8)	
Medical history, n (%)			0.421[c]
No	14 (70)	15 (60)	
Diabetes	4 (20)	2 (8)	
Hypertension	1 (5)	5 (20)	
Anemia	0 (0)	1 (4)	
Asthma	1 (5)	1 (4)	
Dysthyroidism	0 (0)	1 (4)	
Number of prenatal visits, n (%)			
No	1 (5)	5 (20)	0.326[c]
2 visits	2 (10)	2 (8)	
3 or more visits	17 (85)	18 (72)	
Gravidity, n (%)			
1 pregnancy	9 (45)	6 (24)	0.409[c]
2 pregnancies	4 (20)	7 (28)	
3 or more pregnancies	7 (35)	12 (48)	
Parity, n (%)			
1 child	11 (55)	10 (40)	0.228[c]
2 children	6 (30)	4 (16)	
3 children	2 (10)	6 (24)	
4 or more children	1 (5)	5 (20)	
Mode of delivery, n (%)			
Caesarian section	5 (25)	12 (48)	0.135[c]
Vaginal section	15 (75)	13 (52)	

[a] non-normally distributed variables; [b] Mann-Whitney test; [c] Fisher's exact test; IUGR – Intrauterine Growth Restriction. Parity refers to the total number of deliveries reaching a viable gestational age

(45 (44-46) cm vs. 46.5 (45-47) cm, p = 0.012). Significant differences in BMI were observed at 6 months (CA) (16.8 (15.6-18.2) kg/m² vs. 18.6 (17-20) kg/m², p = 0.013), and at 24 months (CA) (16.6 (15.2-17.6) kg/m² vs. 17.6 (16.8-18.6) kg/m², p = 0.029).

The medians of the four anthropometric indices according to the WHO growth charts

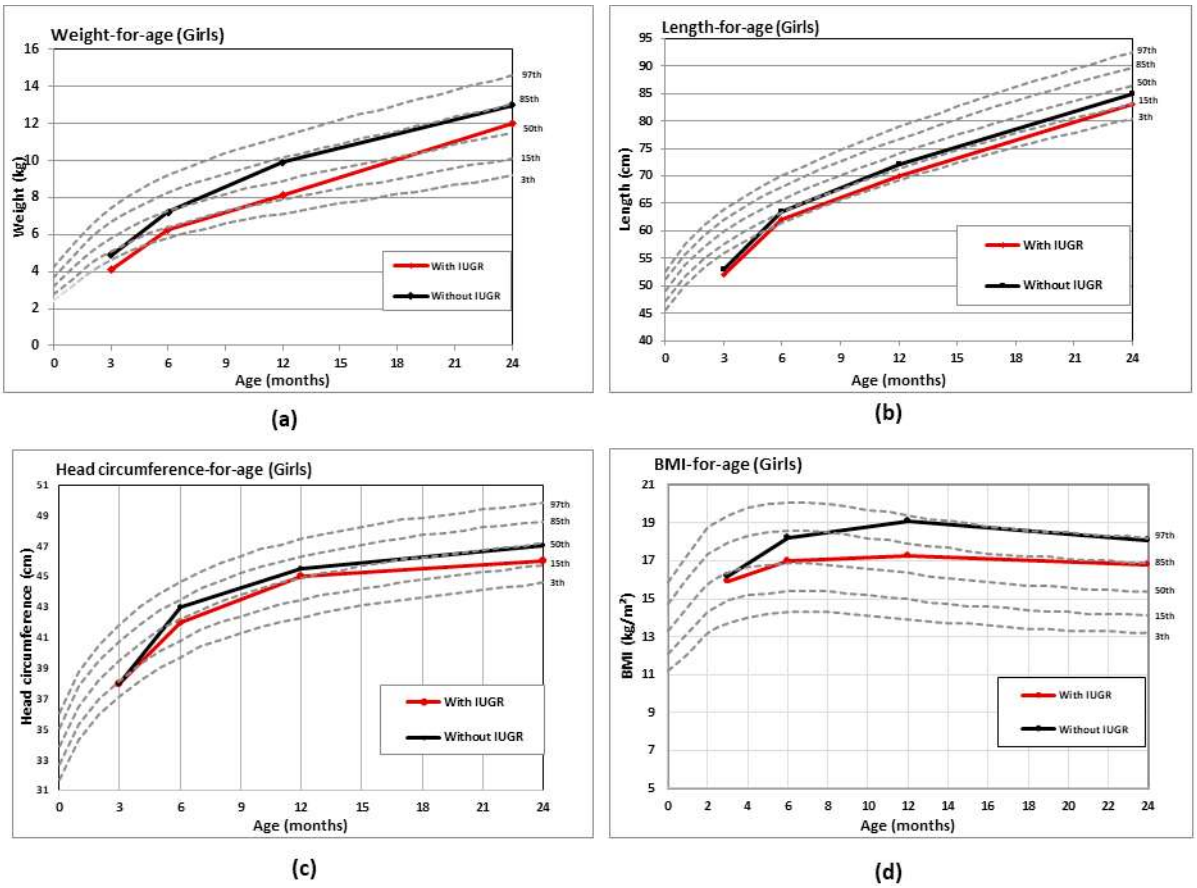
Figures 1 and 2 illustrate the growth trajectories of preterm infants from 3 to 24 months of corrected age (CA), categorized by their intrauterine growth status. To ensure alignment with the WHO growth references [20], all anthropometric data were plotted from three months (CA), the point where preterm trajectories begin to converge with term-born standards. The data show that head circumference (HC) demonstrated the most rapid recovery (Figure 1c). Without-IUGR infants tracked between the 15th and 50th percentiles from six months onwards, while those with IUGR reached the normal range for HC by six months (CA).

In contrast, the recovery of weight and length followed a more protracted course. Preterm girls without IUGR showed a steep upward trajectory in weight (Figure 1a), crossing percentiles to reach the 85th percentile by 12 months (CA). However, those with IUGR remained near the 3rd percentile until six months (CA), achieving normalization between 10 and 12 months (CA). Catch-up in length (Figure 1b) was more gradual; while without-IUGR infants reached the 50th percentile by 24 months, the IUGR group consistently tracked at lower percentiles throughout the observation period. The evolution of BMI-for-age

Table 2. Neonatal characteristics

Neonatal characteristics	Population N = 45		p-value
	Without IUGR n = 20	With IUGR n = 25	
Sex, n (%)			
Male	6 (30)	14 (56)	0.131[a]
Female	14 (70)	11 (44)	
Gestational age (weeks)	33 (30-36)	35 (33-36)	< 0.001[a]
Birth anthropometry			
Weight (g)	1722 ± 414	1438 ± 240	0.006[b]
Height (cm)	41.2 ± 3.98	40 ± 3.64	0.303[b]
Head circumference (cm)	30 (28-32)	29 (27-30)	0.066[a]
Discharge anthropometry			
Weight (g)	1762 ± 306	1660 ± 176	0.169[b]
Height (cm)	42.7 ± 3.48	42.3 ± 2.89	0.678[b]
Head circumference (cm)	30 (29-31.3)	31 (29-31.5)	0.872[a]
Length of hospital stay (days)	18 (5-52)	22 (4-54)	0.298[a]
Age at start of enteral feeding (days)	1 (1-2)	2 (1-2)	0.654[a]

The data are presented as means ± SDs for normally distributed continuous variables, median (25th, 75th percentiles) for nonnormally distributed variables, and n (%) for categorical variables; [a]Mann-Whitney test; [b]Student's exact test



The black curve represents preterm infants without intrauterine growth restriction (IUGR), and the red curve represents those with IUGR

Figure 1. Medians of anthropometric indices according to WHO growth curves for girls in the two subgroups [20]: (a) weight evolution; (b) length gain; (c) head circumference; (d) body mass index

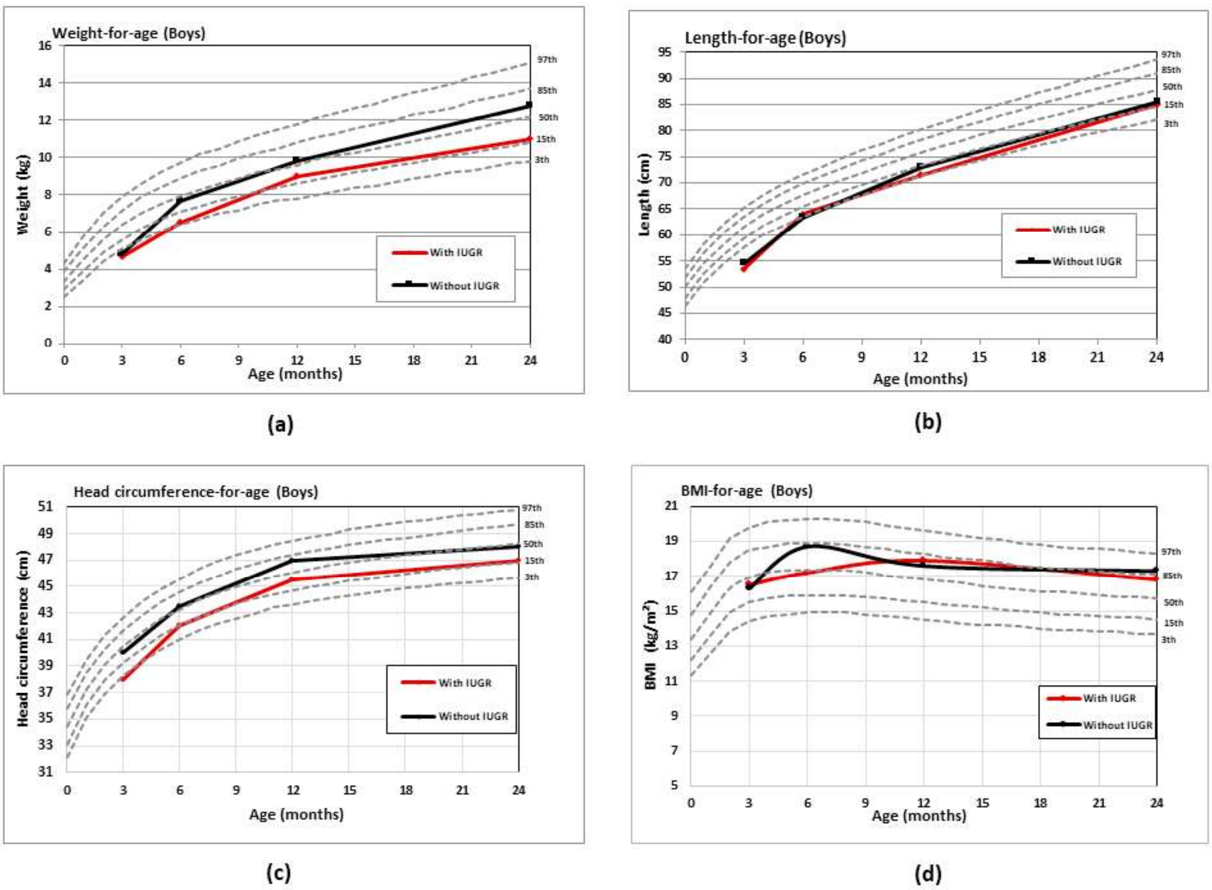
(Figure 1d) showed that values remained within the 15th to 85th percentiles during the first year of life. However, a sharp increase was observed at 24 months (CA). At this stage, the average BMI for infants without IUGR surpassed the 97th percentile, while the IUGR group reached the 85th-97th percentile range, reflecting a significant upward crossing of percentiles at the end of the second year.

Figure 2 illustrates the growth trajectories for preterm boys from 3 to 24 months (CA). Data were plotted from three months (CA) to align with WHO references.

Head circumference (HC) showed rapid recovery (Figure 2c); boys without IUGR tracked between the 15th and 50th percentiles from six months onwards, while the IUGR group reached the normal range by six months (CA). In terms of somatic growth, weight and length followed a more gradual trend. Boys without IUGR showed a steady weight increase (Figure 2a), crossing the 50th percentile by 6 months and approaching the 85th by 24 months. Conversely, boys with IUGR tracked along lower percentiles, with weight stabilizing above the 3rd percentile only after 10-12 months (CA). Recovery in length (Figure 2b) was the most protracted, with the IUGR group remaining near or below the 15th percentile throughout the study. Regarding BMI-for-age (Figure 2d), values remained within the 15th to 85th percentiles during the first year. However, a notable increase occurred at 24 months (CA), where the non-IUGR group reached the 97th percentile.

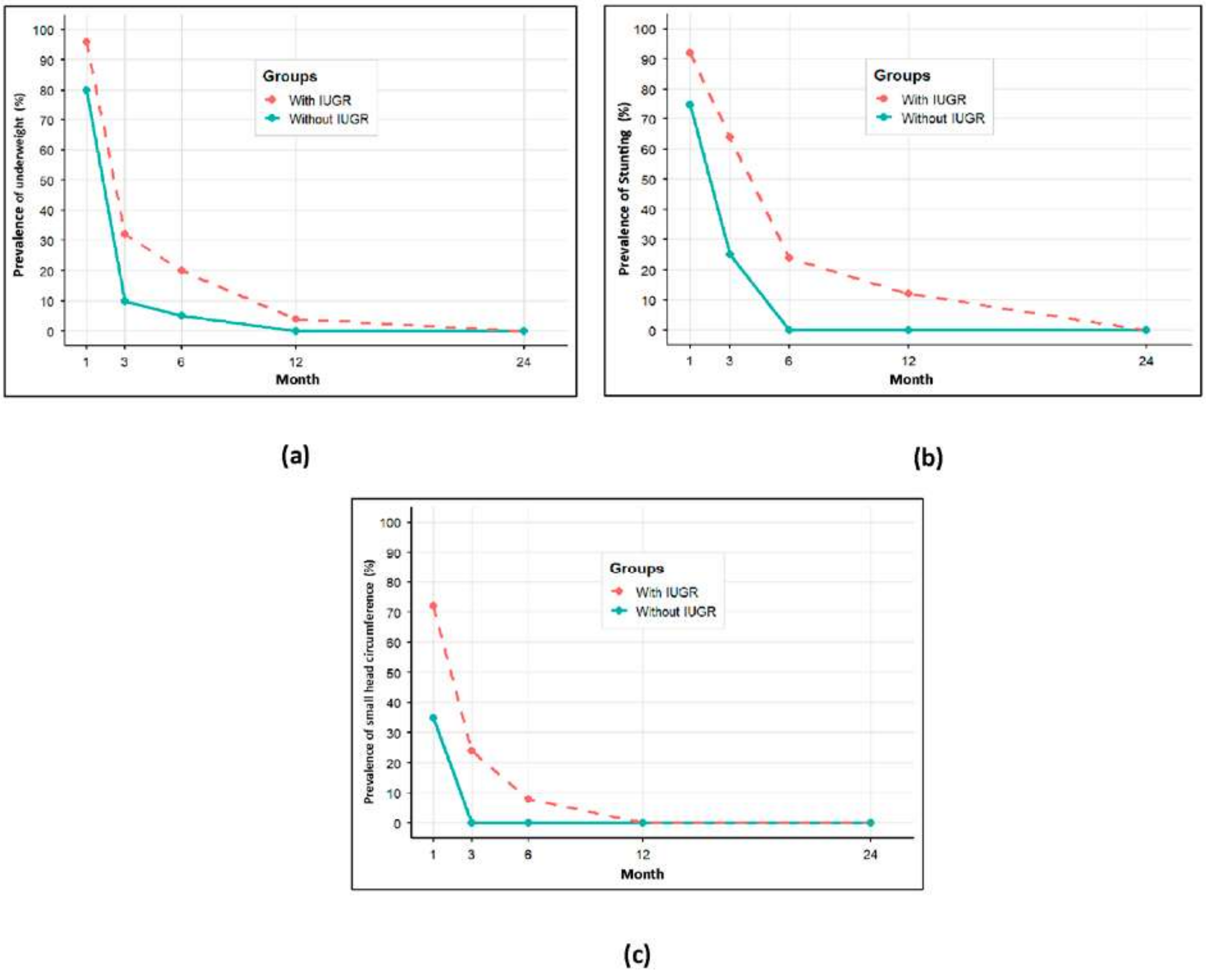
Prevalence of growth restriction

In addition to comparing anthropometric indices, the temporal evolution of growth restriction was analyzed between the two groups, as shown in (Figure 3). Among children without IUGR, at 1 month (CA), 80% had growth retardation in terms of weight (Figure 3a), 75% had growth retardation in terms of height (Figure 3b), and 35% had growth retardation in terms of head circumference (Figure 3c). By 3 months (CA), these prevalences began to decline: 10% of this group had weight retardation at 3a, 25% had stunted at 3b, and the entire group had normal



The black curve represents preterm infants without intrauterine growth restriction (IUGR), and the red curve represents those with IUGR

Figure 2. Medians of anthropometric indices according to WHO growth curves for boys in the two subgroups [20]: (a) weight evolution; (b) length gain; (c) head circumference; (d) body mass index



Infants are categorized as "With IUGR" or "Without IUGR" on the basis of intrauterine growth status; months with no affected infants are represented as 0%, and the y-axis ranges from 0-100%; lines represent the percentage of infants with EUGR for each parameter

Figure 3. Evolution of the prevalence of extrauterine growth restriction (EUGR) in preterm infants from 1 month (CA), to 24 months (CA): (a) weight (underweight), (b) length/height (stunted), (c) head circumference (small head circumference)

head circumference at 3c. From 12 months (CA) to 24 months (CA), the entire group had normal weight, height, and head circumference. Among the children with IUGR, 96% had growth retardation in terms of weight at 3a, 92% in terms of height at 3b and 72% in terms of head circumference at 3c at 1 month (CA). By 3 months (CA), these rates had begun to decline, with 64% experiencing weight retardation at 3a, 24% height retardation at 3b, and 8% head circumference retardation at 3c.

By 6 months (CA), 20% of the children had weight retardation at 3a, 24% had stunting at 3b and 8% had head circumference retardation at 3c. By 12 months (CA), only 4% of the children had weight retardation at 3a, 12% had stunted at 3b and the entire group had a normal head circumference at 3c. By 24 months (CA), the entire group had normal weight, height, and head circumference.

Feeding practices at 3 and 6 months and anthropometric indices

At 3 and 6 months (CA), anthropometric indices were compared between preterm infants receiving maternal (exclusive or mixed) or artificial feeding. The data are presented as the median in (Table 3). At 3 months (CA), there were no statistically significant differences in weight, length or head circumference between the groups, (weights: 4575 g (4005-4978) vs. 5085 g (3905-5590), p = 0.322*)*. Height: 53 cm (51-54) vs. 54 cm (50.5-56.5), p = 0.873. HC: 38 cm (38-40) vs. 38 cm (36-40.5), p = 0.925. At 6 months (CA), infants receiving maternal feeding presented a slightly higher median weight than did those receiving artificial feeding, although the differences were small (7016 g (6462-7565) vs. 6655 g (6170-7440), p = 0.32).

At 3 months (CA), the prevalence of weight-based EUGR was lower among premature infants receiving maternal feeding than among those receiving artificial feeding. Specifically, 6 (17.6%) out of 34 infants in

Table 3. Anthropometric indices in preterm infants according to type of feeding practices at 3 and 6 month (CA)

Corrected age	Maternal feeding	Weight (g)	p-value	Height (cm)	p-value	HC (cm)	p-value
Month 3	Yes (n = 34)	4575 (4005-4978)	0.322	53 (51-54)	0.873	38 (38-40)	0.925
	No (n = 11)	5085 (3905-5590)		54 (50.5-56.5)		38 (36-40.5)	
Month 6	Yes (n = 20)	7016 (6462-7565)	0.320	62.5 (60-64.2)	0.334	42.5 (42-44)	1.000
	No (n = 25)	6655 (6170-7440)		64 (61-65)		43 (32-44)	

The data are presented as medians (25th, 75th percentiles); Yes – maternal feeding (exclusive or partial); No – artificial feeding; HC – head circumference; For each parameter, the Mann-Whitney test was used for calculation; A p-value < 0.05 was considered statistically significant

the maternal feeding group were EUGR, compared to 4 (36.4%) out of 11 infants in the artificial feeding group. However, this difference did not reach statistical significance (p = 0.227). Similarly, the prevalence of EUGR for length and HC was lower in infants receiving maternal feeding, although these differences also lacked statistical significance (p = 1.000 and p = 0.145, respectively). At 6 months (CA), the prevalence of weight discordance remained lower among the maternal feeding group than among the artificial feeding group. Among the 20 infants receiving maternal feeding, 1 (5%) was EUGR, whereas 5 (20%) of the 25 infants receiving artificial feeding were EUGR. However, this difference did not reach statistical significance (p = 0.20).

DISCUSSION

The present study provides a longitudinal perspective on the growth of preterm IUGR infants in a Moroccan cohort over the first 24 months of corrected age (CA). As illustrated in our growth charts (Figures 2 and 3 (a, b, and c)), infants born with IUGR (red lines) consistently maintain lower median values for weight, height, and head circumference (HC) compared to the non-IUGR group (black line) throughout the follow-up period. This persistent gap confirms that the initial deficit established in utero is not fully resolved during the "first 1000 days" of life, a period recognized as the most critical window for long-term health and human capital [21]. These findings align with global data from low- and middle-income countries, where the combination of prematurity and growth restriction significantly increases the risk of chronic undernutrition and stunting throughout early childhood [22]. Our findings regarding the difficulty of achieving complete recovery are strongly supported by the work of Vizzari et al. [23], who demonstrated that catch-up growth in small-for-gestational-age (SGA) infants is often a protracted process limited by the severity of the initial intrauterine insult. While Han et al. [24] reported a high catch-up rate of 85% by 24 months, our data suggest a more challenged recovery in the North African context. This discrepancy may be attributed to the biological constraint hypothesis; as suggested by Calek et al. [25], infants with true pathological IUGR face distinct metabolic and body composition challenges compared to those who are simply constitutionally small. Such early growth deficits can persist long-term, as evidenced by Saigal et al. [26], whose longitudinal research shows that growth trajectories of extremely low birth weight infants are often affected well into young adulthood.

In alignment with this perspective, the prevalence of underweight and stunting in our cohort remained significantly higher in the IUGR group, particularly during the first year. This indicates that the recovery window is not limited to the first few months but extends deep into the second year of life. By utilizing the WHO Child Growth Standards [20], we ensured that this lag was evaluated against a global benchmark. However, the clinical interpretation of this persistent deficit remains a subject of intense debate. While traditional models might view slow catch-up as a failure, the growth acceleration hypothesis (Singhal et al. [27]) suggests that the slower velocity observed in our IUGR cohort may paradoxically serve as a protective mechanism against the metabolic programming of obesity and cardiovascular disease in adulthood. This highlights a critical clinical dilemma: the need to promote sufficient growth for neurodevelopmental optimization, as indicated by our findings on cranial recovery, while avoiding the adiposity rebound associated with rapid weight gain. Consequently, our results emphasize the necessity for prolonged, nuanced clinical surveillance that moves beyond simple weight targets to ensure a steady, balanced recovery throughout the first 1000 days of life.

The persistence of growth deficits throughout the second year of life naturally raises question regarding the role of early nutritional interventions in modifying these trajectories. In our study, feeding practices were evaluated to determine their influence on catch-up kinetics and the prevalence of EUGR. For the purpose of this analysis, infants receiving any proportion of breast milk were categorized under maternal feeding (including exclusive and partial feeding), reflecting the clinical reality that even partial exposure to human milk provides essential bioactive components, such as insulin-like growth factors (IGF-1), hormones, and immunoglobulins [28, 29], which act as critical signalling molecules for the somatic and metabolic development of preterm infants [30]. However, these mechanisms operate within a highly complex biological network involving thousands of genes and layers of epigenetic regulation. Rather than acting through isolated pathways, these factors contribute collectively to maintaining shared maternal-foetal homeostasis, thereby governing the intricate molecular adaptations that occur in both organisms [31, 32].

While the differences in median weight, height, and HC between feeding groups did not reach formal statistical significance at 3 and 6 months (CA), important clinical trends emerged. At 3 months (CA), infants receiving human milk exhibited a substantially lower prevalence of being underweight (17.6%) compared to those exclusively formula-fed (36.4%). A similar protective trend was observed for HC at 3 months, with an EUGR rate of 8.8% in the maternal feeding group versus 27.3% in the formula group. By 6 months CA, the prevalence of underweight remained four times lower in the maternal feeding group (5% vs. 20%). These findings suggest that while human milk supports a growth velocity comparable to formula, it may offer a crucial clinical advantage in reducing the severity of postnatal growth failure during the first 1000 days. Our results offer a necessary nuance to a study, who reported that breast milk did not significantly reduce EUGR prevalence at discharge [33]. This discrepancy is likely rooted in population differences. This study focused exclusively on very low birth weight (VLBW) infants with extreme metabolic demands. In our broader IUGR population, human milk appears to act as a metabolic regulator. This observation aligns with previous work demonstrating that early exposure to human milk modulates postnatal growth quality and tissue accretion patterns in preterm infants, suggesting a programming effect that may translate into improved long-term metabolic health rather than simply enhanced weight gain [34]. This concept is further supported by reviews indicating that human milk feeding in preterm populations is associated with growth patterns compatible with healthier cardio metabolic programming [35], even in the absence of marked differences in early anthropometric recovery. Furthermore, breastfeeding has been shown to exert a protective effect on the development of risk factors associated with metabolic syndrome in infants born preterm, specifically by influencing lipid profiles and adiponectin levels [36].

Furthermore, the favorable trend in HC attainment observed in our maternal feeding group is of significant prognostic value. This study [37] indicates that early cranial catch-up specifically when supported by human milk, is a superior predictor of white matter development and long-term neurocognitive scores compared to rapid weight gain. This is further corroborated by research [38], who demonstrated that the nutritional quality of human milk is uniquely linked to brain volume and metabolic safety. By achieving somatic growth equivalent to formula-fed infants without the metabolic stress of hypercaloric artificial feeding [39], human milk supports the "brain-sparing" effect through a more physiological pathway. This reinforces the argument that nutritional success in IUGR cohorts should be measured by the quality of catch-up prioritizing neurodevelopmental potential and metabolic health, rather than purely through absolute anthropometric parity.

The metabolic adaptations and growth responses observed postnatally are inextricably linked to the intrauterine environment and the timing of delivery. In our study, maternal characteristics and clinical management emerged as critical precursors to the infants' long-term trajectories. Our analysis revealed a significant correlation between advanced maternal age and the incidence of IUGR, a finding that aligns with contemporary obstetric literature. This association is largely attributed to the age-related decline in placental efficiency and increased uterine artery resistance. According to previous research [40], older maternal age is often linked to placental angiogenic dysfunction, which restricts the flow of essential nutrients and oxygen, thereby establishing the pathological basis for fetal growth restriction.

A notable observation in our cohort was the higher gestational age of IUGR infants compared to their non-IUGR counterparts. This discrepancy reflects a deliberate clinical strategy of fetal rescue. In managing growth-restricted foetuses, clinicians often attempt to prolong the pregnancy to maximize pulmonary maturity and minimize the risks of severe prematurity, even when the intrauterine environment is suboptimal. As detailed in the literature [41], this strategy requires a delicate balance; while extending the pregnancy can prevent neonatal respiratory distress, it also prolongs the foetus's exposure to chronic hypoxia and malnutrition. This prolonged deprivation may induce epigenetic modifications in growth-related genes, further cementing the growth lag observed postnatally. Furthermore, current scientific evidence [42] emphasize that postnatal catch-up in IUGR infants is not merely a continuation of the fetal trajectory but a distinct phase of metabolic adaptation. The fact that our IUGR group was born at a later gestational age yet still exhibited significant postnatal stunting reinforces the idea that the insult of IUGR is profound and enduring. It suggests that while the fetal rescue strategy is successful in terms of immediate survival and respiratory health, it does not mitigate the long-term biological programming that restricts anthropometric attainment. This highlights the critical need for individualized neonatal follow-up that accounts for both the severity of the IUGR and the maternal context in which it developed.

A major strength of this study lies in the systematic comparison between preterm infants with and without IUGR, allowing for a robust assessment of how intrauterine growth restriction independently shapes postnatal trajectories. The longitudinal design, spanning up to 24 months of corrected age, provides a comprehensive view of the first 1000 days, while the analysis of feeding methods offers an original clinical perspective within a North African cohort. However, some limitations should be noted. The sample size remains relatively limited, which can affect the statistical power of certain subgroup comparisons, a common challenge in long-term neonatal follow-up. Furthermore, the findings of studies focused exclusively on very low birth weight (VLBW) infants, such as study [34], differ from ours primarily due to the distinct metabolic demands of that specific population compared to our broader preterm cohort. This methodological divergence necessitates a nuanced comparison of nutritional outcomes. Finally, while anthropometry is a validated proxy, the use of advanced body composition techniques, such as deuterium isotope dilution, would provide a more granular understanding of the quality of mass gain (lean vs. fat mass) in these infants.

CONCLUSION

In conclusion, our data confirm that preterm infants born with IUGR in this Moroccan cohort maintain significant growth deficits, compared to non-IUGR peers. While the findings suggest that maternal milk may help mitigate the severity of postnatal growth failure, this observation, along with the proposed influences of fetal rescue strategies, remains a clinical interpretation that requires validation through larger studies. Given the limited sample size and specific regional context, these results should be generalized with caution. Nevertheless, this study underscores the necessity for prolonged, individualized clinical surveillance during the first 1000 days.

Acknowledgements

We would like to thank all the mothers and newborns who participated in this study. Their cooperation was invaluable and made this research possible. We also acknowledge the support of the medical staff and nurses at the National Reference Center for Neonatology and Nutrition in Rabat for their assistance in data collection.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. World Health Organization. Preterm birth [Internet]. [cited 2025 Sept 23]. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth.
2. Ohuma EO, Moller A-B, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. The Lancet. 2023;402(10409):1261-1271. doi: 10.1016/S0140-6736(23)00878-4.
3. Yitayew M, Chahin N, Rustom S, Thacker LR, Hendricks-Muñoz KD. Fenton vs. Intergrowth-21st: Postnatal Growth Assessment and Prediction of Neurodevelopment in Preterm Infants. Nutrients. 2021;13(8):2841. doi: 10.3390/nu13082841.
4. Villamor-Martinez E, Kilani MA, Degraeuwe PL, Clyman RI, Villamor E. Intrauterine Growth Restriction and Patent Ductus Arteriosus in Very and Extremely Preterm Infants: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2019;10:58. doi: 10.3389/fendo.2019.00058.
5. Cheikh Ismail L, Mohamad MN, Ohuma EO, ElHalik MS, Dash SK, Osaili TM, et al. Comparison of INTERGROWTH- 21st and Fenton growth standards to assess size at birth and at discharge in preterm infants in the United Arab Emirates. BMC Pediatr. 2024;24(1):814. doi: 10.1186/s12887-024-04928-3.
6. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59. doi: 10.1186/1471-2431-13-59.
7. Wang L, Lin X-Z, Shen W, Wu F, Mao J, Liu L, et al. Risk factors of extrauterine growth restriction in very preterm infants with bronchopulmonary dysplasia: a multi-center study in China. BMC Pediatr. 2022;22(1):363. doi: 10.1186/s12887-022-03405-z.
8. Shen W, Wu F, Mao J, Liu L, Chang Y-M, Zhang R, et al. Analysis of "true extrauterine growth retardation" and related factors in very preterm infants—A multicenter prospective study in China. Front Pediatr. 2022;10:876310. doi: 10.3389/fped.2022.876310.
9. Anggareni KT, Sidiartha IGL, Artana IWD, Suwarba IGNM, Hartawan INB, Gustawan IW. Prevalence and factors associated with extrauterine growth restriction in premature infants. Paediatr Indones. 2024;64(5):405-411. doi: 10.14238/pi64.5.2024.405-11.
10. John MJ, Varughese PV, Sharma M. A Prospective Study of Incidence and Factors Associated with Extrauterine Growth Restriction amongst Pre-term

Neonates. Hamdan Med J. 2023;16(3):234. doi: 10.4103/hmj.hmj_52_23.

11. İşcan B. Postnatal growth and extrauterine growth retardation (EUGR) in extremely low gestational age newborns (ELGAN) with a 2-year follow-up. Trends Pediatr. 2025;6(1):33-39. doi: 10.59213/TP.2025.206.
12. Kozonis A, Papadoliopoulou M, Margaris I. Fetal Growth Restriction, Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder-Connecting the Dots: A Narrative Review. Children (Basel). 2025;13(1):9. doi: 10.3390/children13010009.
13. Peila C, Spada E, Giuliani F, Maiocco G, Raia M, Cresi F, et al. Extrauterine Growth Restriction: Definitions and Predictability of Outcomes in a Cohort of Very Low Birth Weight Infants or Preterm Neonates. Nutrients. 2020;12(5):1224. doi: 10.3390/nu12051224.
14. Pathways.org. Prematurity and 'Corrected Age': What Does it Mean? [Internet]. [cited 2026 Jan 28]. Available from: https://pathways.org/adjusting-age-for-prematurity.
15. World Health Organization. Exclusively breastfeed for 6 months [Internet]. [cited 2026 Jan 28]. Available from: https://www.emro.who.int/nutrition/breastfeeding/?utm_source=chatgpt.com.
16. UNICEF. Mixed Milk Feeding (0-5 months) [Internet]. [cited 2026 Jan 28]. Available from: https://data.unicef.org/indicator-profiles/NT_BF_MIXMF/
17. Patnode CD, Henrikson NB, Webber EM, Blasi PR, Senger CA, Guirguis-Blake JM. Breastfeeding and Health Outcomes for Infants and Children [Internet]. Agency for Healthcare Research and Quality (US), 2025. Appendix A, Key Definitions. [cited 2026 Jan 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK615270/.
18. Maternal, Perinatal, and Pediatric Nutrition. Curr Dev Nutr. 2028;2(11):nzy040. doi: 10.1093/cdn/nzy040.
19. World Health Organization. WHO child growth standards: training course on child growth assessment [Internet]. [cited 2026 Jan 28]. Available from: https://www.who.int/publications/i/item/9789241595070.
20. World Health Organization. The WHO Child Growth Standards [Internet]. [cited 2025 Oct 8]. Available from: https://www.who.int/tools/child-growth-standards/standards.
21. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 2008;371(9609):340-357. doi: 10.1016/S0140-6736(07)61692-4.
22. Christian P, Lee SE, Donahue Angel M, Adair LS, Arifeen SE, Ashorn P, et al. Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries. Int J Epidemiol. 2013;42(5):1340-1355. doi: 10.1093/ije/dyt109.
23. Vizzari G, Morniroli D, Tiraferri V, Macchi M, Gangi S, Consales A, et al. Postnatal growth of small for gestational age late preterm infants: determinants of catch-up growth. Pediatr Res. 2023;94(1):365-370. doi: 10.1038/s41390-022-02402-3.
24. Han J, Jiang Y, Huang J, Zhang Y, Zhang Y, Zhang Y, et al. Postnatal growth of preterm infants during the first two years of life: catch-up growth accompanied by risk of overweight. Ital J Pediatr. 2021;47(1):66. doi: 10.1186/s13052-021-01019-2.
25. Calek E, Binder J, Palmrich P, Eibensteiner F, Thajer A, Kainz T, et al. Effects of Intrauterine Growth Restriction (IUGR) on Growth and Body Composition Compared to Constitutionally Small Infants. Nutrients. 2023;15(19):4158. doi: 10.3390/nu15194158.
26. Saigal S, Stoskopf B, Streiner D, Paneth N, Pinelli J, Boyle M. Growth Trajectories of Extremely Low Birth Weight Infants From Birth to Young Adulthood: A Longitudinal, Population-Based Study. Pediatr Res. 2006;60(6):751-758. doi: 10.1203/01.pdr.0000246201.93662.8e.
27. Singhal A. Long-Term Adverse Effects of Early Growth Acceleration or Catch-Up Growth. Ann Nutr Metab. 2017;70(3):236-240. doi: 10.1159/000464302.
28. Suganuma M, Rumbold AR, Miller J, Chong YF, Collins CT. A Systematic Review and Meta-Analysis of Human Milk Feeding and Short-Term Growth in Preterm and Very Low Birth Weight Infants. Nutrients. 2021;13(6):2089. doi: 10.3390/nu13062089.
29. Ballard O, Morrow AL. Human Milk Composition: Nutrients and Bioactive Factors. Pediatr Clin North Am. 2013;60(1):49-74. doi: 10.1016/j.pcl.2012.10.002.
30. Lönnerdal B. Bioactive proteins in human milk: mechanisms of action. J Pediatr. 2010; 156(2 Suppl):S26-30. doi: 10.1016/j.jpeds.2009.11.017.
31. Fowden AL, Giussani DA, Forhead AJ. Intrauterine programming of physiological systems: causes and consequences. Physiology (Bethesda). 2006;21:29-37. doi: 10.1152/physiol.00050.2005.
32. Moore G, Oakey R. The role of imprinted genes in humans. Genome Biol. 2011;12(3):106. doi: 10.1186/gb-2011-12-3-106.
33. Modi P, Ramji S. Evaluating the nutritional status of preterm very low birth weight infants at discharge: a prospective cohort study. Int J Contemp Pediatr. 2025;12(2):194-199. doi: 10.18203/2349-3291.ijcp20250021.
34. Giannì ML, Consonni D, Liotto N, Roggero P, Morlacchi L, Piemontese P, et al. Does Human Milk Modulate Body Composition in Late Preterm Infants at Term-Corrected Age? Nutrients. 2016;8(10):664. doi: 10.3390/nu8100664.
35. Cerasani J, Ceroni F, De Cosmi V, Mazzocchi A, Morniroli D, Roggero P, et al. Human Milk Feeding and Preterm Infants' Growth and Body Composition: A Literature Review. Nutrients. 2020;12(4):1155. doi: 10.3390/nu12041155.
36. Ikeda N, Shoji H, Murano Y, Mori M, Matsunaga N, Suganuma H, et al. Effects of breastfeeding on the risk factors for metabolic syndrome in preterm infants. J Dev Orig Health Dis. 2014;5(6):459-464. doi: 10.1017/S2040174414000397.
37. Belfort MB, Anderson PJ, Nowak VA, Lee KJ, Molesworth C, Thompson DK, et al. Breast milk feeding, brain development, and neurocognitive

outcomes: a 7-year longitudinal study in infants born <30 weeks' gestation. J Pediatr. 2016;177:133-139.e1. doi: 10.1016/j.jpeds.2016.06.045.

38. Isaacs EB, Fischl BR, Quinn BT, Chong WK, Gadian DG, Lucas A. Impact of breast milk on intelligence quotient, brain size, and white matter development. Pediatr Res. 2010;67(4):357-362. doi: 10.1203/PDR.0b013e3181d026da.
39. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. Lancet. 2001;357(9254):413-419. doi: 10.1016/S0140-6736(00)04004-6.
40. Biagioni EM, May LE, Broskey NT. The impact of advanced maternal age on pregnancy and offspring health: A mechanistic role for placental angiogenic growth mediators. Placenta. 2021;106:15-21. doi: 10.1016/j.placenta.2021.01.024.
41. Tozzi MG, Moscuzza F, Michelucci A, Lorenzoni F, Cosini C, Ciantelli M, et al. ExtraUterine Growth Restriction (EUGR) in Preterm Infants: Growth Patterns, Nutrition, and Epigenetic Markers. A Pilot Study. Front Pediatr. 2018;6:408. doi: 10.3389/fped.2018.00408.
42. Hay WW, MD J, Lucas A, Heird WC, Ziegler E, Levin E, et al. Workshop Summary: Nutrition of the Extremely Low Birth Weight Infant. Pediatrics. 1999;104(6):1360-1368. doi: 10.1542/peds.104.6.1360.

Received: 05.11.2025
Revised: 16.01.2026
Accepted: 30.01.2026