9ο Πανελλήνιο Συνέδριο Νεογνολογίας
19-21 Μαΐου 2023 Ξενοδοχείο Crowne Plaza Αθήνα

Εξατομικευμένη ενίσχυση του μητρικού γάλακτος

Λιθοξοπούλου Μαρία,
Επίκουρη Καθηγήτρια Παιδιατρικής και Νεογνολογίας,
Β΄Νεογνολογική Κλινική και ΜΕΝΝ
Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης
Νοσοκομείο «Παπαγεωργίου»

No conflicts of interest to resolve.

Θέματα της Παρουσίασης

- ✓ Ενισχυμένο ή μη ενισχυμένο Μητρικό Γάλα
- ✓ Τύποι ενίσχυσης
- ✓ Πρώιμη ή καθυστερημένη ενίσχυση
- ✓ Σταθερή vs εξατομικευμένη ενίσχυση
- ✓ Πετυχαίνουμε την επιθυμητή τροχιά και ρυθμό αύξησης;
- ✓ Μακροπρόθεσμες επιπτώσεις

Μητρικό Γάλα

- Ιδανική τροφή για το πρόωρο-ειδικά το VLBW

  Ανοσολογικά, νευροαναπτυξιακά και γαστρεντερολογικά

  Ανοχή και απορρόφηση εντερικής διατροφής

  Μείωση ΝΕΚ, όψιμης σηψαιμίας και ROP
- Αυξημένες ενεργειακές ανάγκες στο κρίσιμο στάδιο αύξησης και ανάπτυξης εκτός μήτρας
- Ολοκλήρωση εμβρυϊκής αύξησης και κάλυψη μεταβολικών αναγκών
- Περιορισμούς όγκου τροφής (νοσηρότητα)

Gila-Diaz, et al . A review of bioactive factors in human breastmilk: A focus on prematurity. Nutrients ***2019***

Εντερική σίτιση προώρου

- Μητρικό γάλα με ενίσχυση

Mothers Own Milk (preterm milk) fortification

- Γάλα δότριας από Τράπεζα ΜΓ με ενίσχυση

Banked Milk (if possible preterm milk) fortification

- Γάλα για πρόωρα

Preterm formula

- Παρεντερική διατροφή ως συμπλήρωμα εντερικής

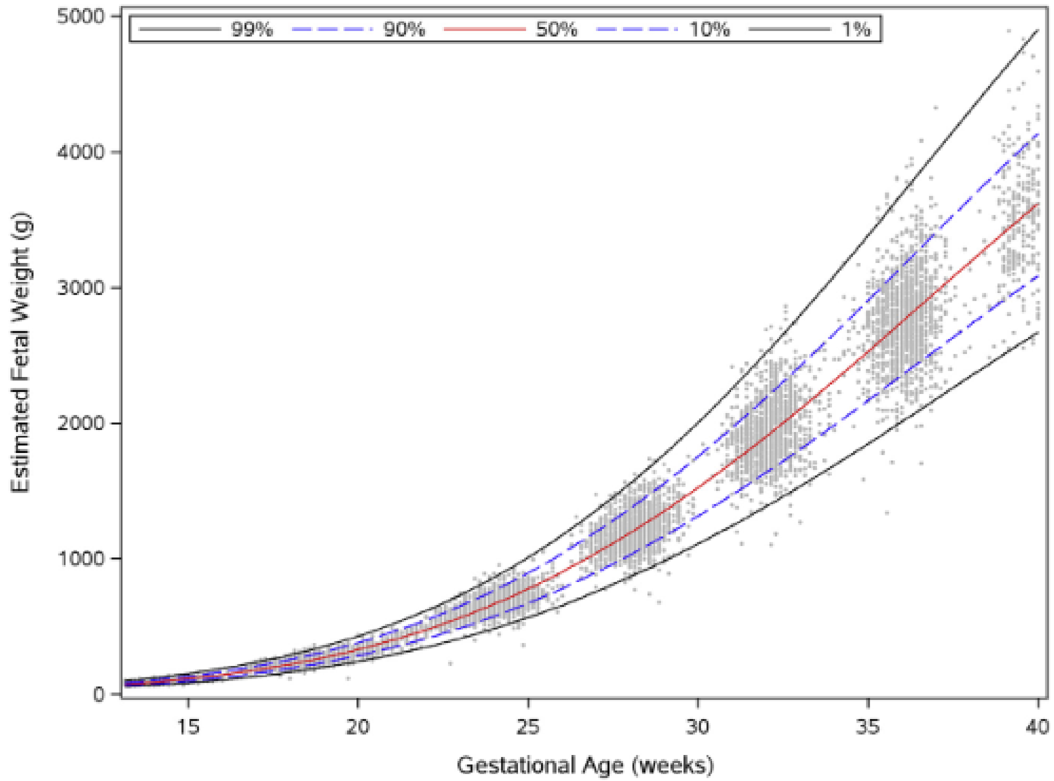
Ποια είναι η αύξηση που αναμένουμε;

Intra-uterine growth curves

Weight, length, head circumference

Well functioning placenta

FIGURE 1
World Health Organization fetal growth chart: estimated fetal weight percentiles



- *Landau-Crangle E, et al.* ***Journal of parenteral and enteral nutrition****. 2018.*
- *Kiserud T, PiaggioG, Carroli G, et al. The* ***World Health Organization fetal growth charts****: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med 2017*
- *J. Stirnemann et al,* ***International estimated fetal weight standards of the INTERGROWTH-21st Project,*** *Ultrasound Obstet Gynecol, 2017*
- Kiserud T, The **World Health Organization fetal growth charts**: concept, findings, interpretation, and application American Journal of Obstetrics & Gynecology, 2018

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

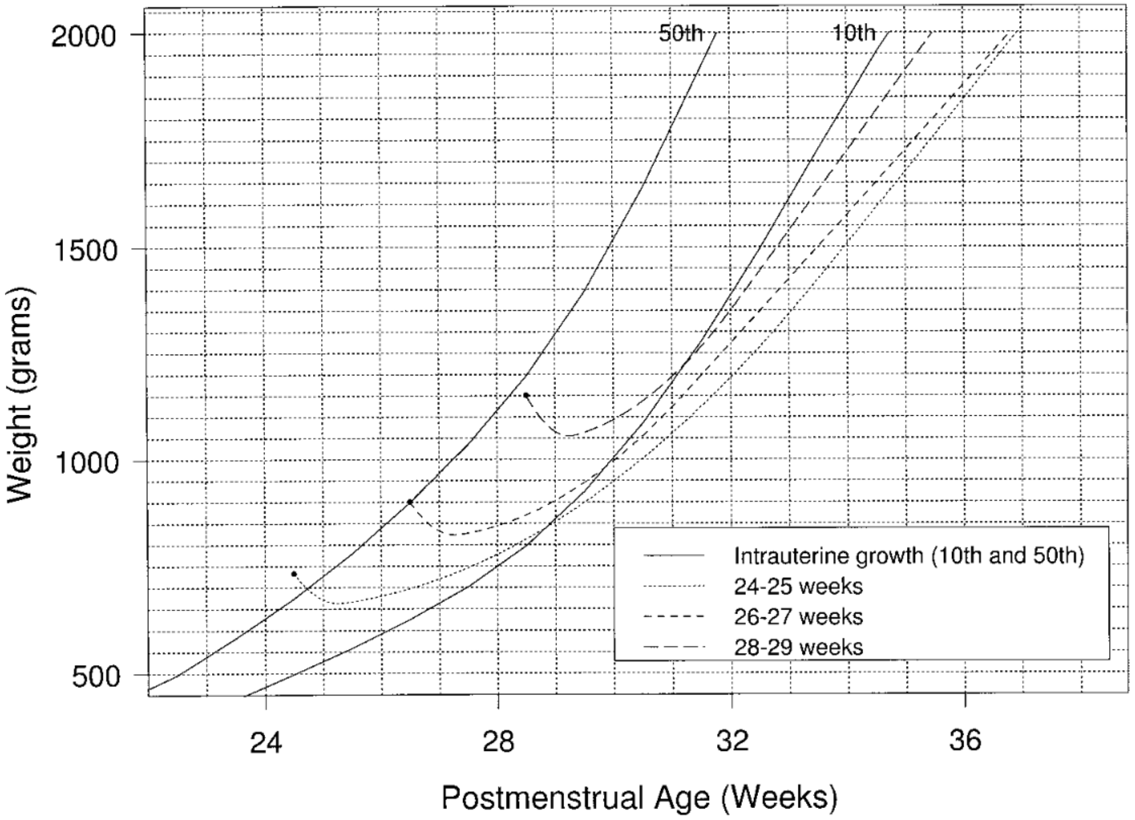
American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Postnatal nutritional management

- Intrauterine rates of fetal growth (15 g/ kg/day)
- Επιβράδυνση ρυθμού αύξησης μετά γέννηση.
- Νευροαναπτυξιακά αποτελέσματα.
- **Prevention** of restriction during hospitalization- important.

Jose Villar, et al, **Monitoring the Postnatal Growth of Preterm Infants: A Paradigm Change**
Pediatrics (2018) 141 (2): e20172467.

Fig 7. Average body weight versus postmenstrual age in weeks for all study infants with gestational ages 24 to 25 weeks (dotted line), 26 to 27 weeks (short dashes), and 28 to 29 weeks (long dashes). The reference intrauterine growth curves were plotted using the smoothed 10th and 50th percentile birth weight data reported by Alexander et al.[22]



Ehrenkranz, R. A., Younes, N., Lemons, J. A., Fanaroff, A. A., Donovan, E. F., Wright, L. L., … Papile, L.-A. (1999). *Longitudinal Growth of Hospitalized Very Low Birth Weight Infants. Pediatrics, 104(2), 280–289.* doi:10.1542/peds.104.2.280

Growth in the Neonatal Intensive Care Unit Influences Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants

Richard A. Ehrenkranz, MD[a], Anna M. Dusick, MD[b], Betty R. Vohr, MD[c], Linda L. Wright, MD[d], Lisa A. Wrage, MPH[e], W. Kenneth Poole, PhD[e], for the National Institutes of Child Health and Human Development Neonatal Research Network

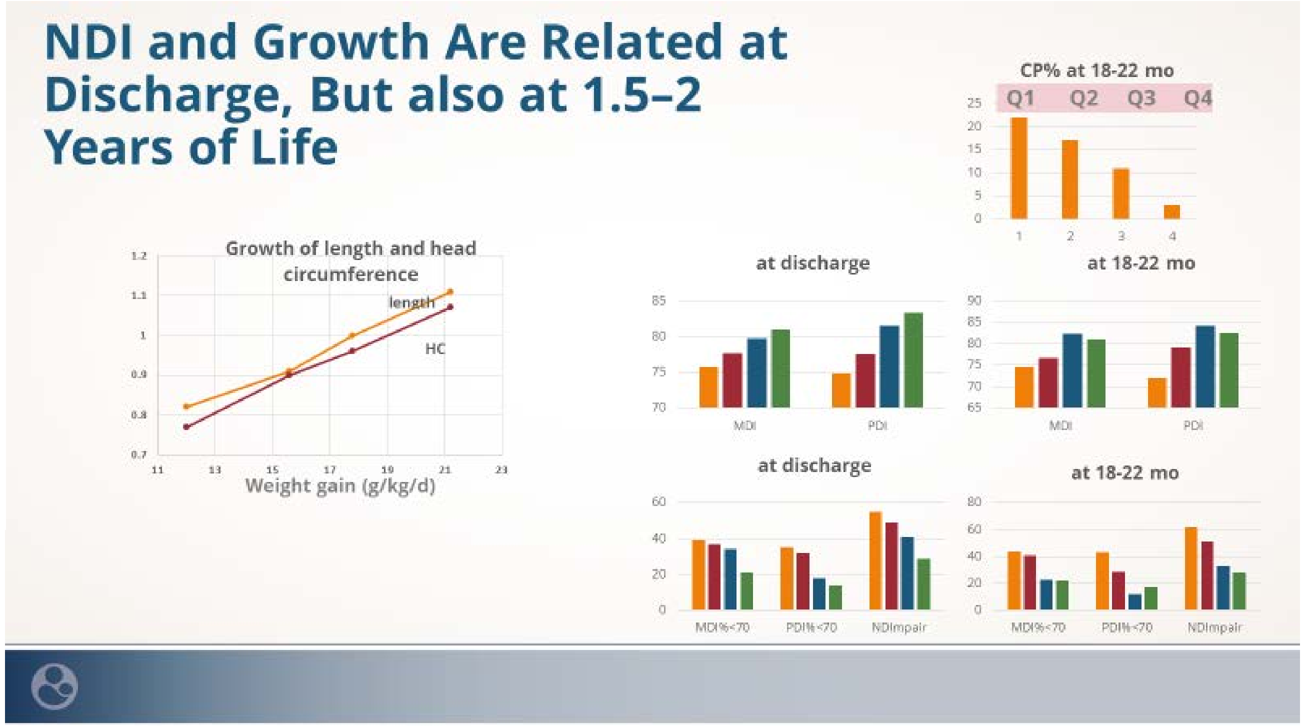
[a]Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; [b]University of Indiana, Indianapolis, Indiana; [c]Department of Pediatrics, Brown University, Providence, Rhode Island; [d]National Institutes of Child Health and Human Development, Bethesda, Maryland; [e]RTI International, Research Triangle Park, North Carolina

Αύξηση ΒΣ σχετίζεται με νευροανάπτυξη διορθωμένη ηλικία 18-22 μηνών

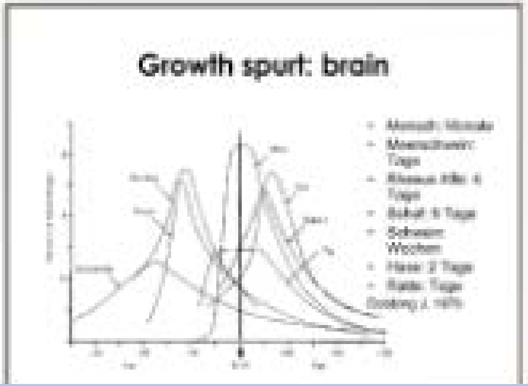
TABLE 3 Outcomes at 18 to 22 Months' Corrected Age According to Weight Gain Quartile

Outcome[a]	Quartile 1 (*n* = 124)	Quartile 2 (*n* = 122)	Quartile 3 (*n* = 123)	Quartile 4 (*n* = 121)	*P*[b]
Weight gain, mean (SD), g/kg per d	12.0 (2.1)	15.6 (0.8)	17.8 (0.8)	21.2 (2.0)	—
Normal neurologic examination	70	77	76	86	<.01
CP, %	21	13	13	6	<.01
MDI	75.7 (18)	77.7 (18)	79.7 (18)	80.9 (15)	.32
MDI < 70, %	39	37	34	21	<.01
PDI	74.8 (19)	77.5 (19)	81.5 (17)	83.3 (14)	<.01
PDI < 70, %	35	32	18	14	<.001
Blind, %					.21
Unilateral	1	1	0	4	
Bilateral	3	1	0	1	
Hearing impairment, %	5	6	3	2	.36
Hearing aids, %	3	3	2	1	.69
Neurodevelopmental impairment, %	55	49	41	29	<.001
Weight <10th percentile, %	58	61	51	46	.03
Length <10th percentile, %	47	43	29	28	<.001
Head circumference <10th percentile, %	31	18	18	22	.098
Rehospitalization, %	63	60	50	45	<.01

Growth velocity during NICU hospitalization effect on neurodevelopmental and growth outcomes at 18 to 22 months' corrected age. (2006)



Neurodevelopment of ELBW Infants Correlates with the Nutritional Intake



M. Lithoxopoulou, et al. Early caloric deprivation in preterm infants affects Bayley-III scales performance at 18–24 months of corrected age ***Research in Developmental Disabilities 91 (2019)*** *103429*

- N=124 ELBW infants
- Mean birth weight 787 ±133 g
- Mean gestational age was 25.9 ±1.6 weeks

TABLE 3 Regression Analysis Week-1 Energy Intake and 18-Month MDI

Variable	b (SE)	*P*	Partial R^2
Birth weight	0.03 (0.01)	.0244	0.06
Male gender	−8.23 (2.90)	.0055	0.09
IVH	−1.51 (6.15)	.8063	0.01
CLD	0.38 (3.14)	.9046	0.00
NEC	−1.99 (3.94)	.6143	0.01
Maternal education, college graduate	4.77 (2.90)	.1036	0.01
Energy, 4.2 kJ (1 kcal)/kg per day	0.46 (0.18)	.0134	0.05

R^2 = 0.23. Adjusted R^2 = 0.18. b (SE) indicates effect size (SE).

TABLE 4 Regression Analysis Week 1 Protein Intake and 18 month MDI

Variable	b (SE)	*P*	Partial R^2
Birth weight	0.03 (0.01)	.0227	0.06
Male gender	−8.72 (2.90)	.0033	0.09
IVH	−2.41 (6.14)	.6948	0.01
CLD	−0.06 (3.14)	.9838	0.00
NEC	−3.17 (3.93)	.4210	0.01
Maternal education, college graduate	4.32 (2.90)	.1397	0.01
Protein, g/kg per day	8.21 (3.67)	.0274	0.04

R^2 = 0.22. Adjusted R^2 = 0.17. b (SE) = effect size (SE).

Each **kcal/kg/d** increases **MDI** by **0.46 points**

Each **g protein/kg/d** increases **Bayley MDI** by **8.2 points**

Stephens, B. E., Walden, R. V., Gargus, R. A., Tucker, R., McKinley, L., Mance, M., Vohr, B. R. (2009). *First-Week Protein and Energy Intakes Are Associated With 18-Month Developmental Outcomes in Extremely Low Birth Weight Infants. PEDIATRICS, 123(5), 1337–1343.*

Διατροφικές Πρακτικές Για Πρόωρα

Κατευθυντήριες οδηγίες και συστάσεις

Ευρωπαϊκής Εταιρείας Παιδιατρικής Γαστρεντερολογίας, Ηπατολογίας Διατροφής (ESPGHAN)

Συστάσεις κλινικής πράξης -έρευνα υψηλής ποιότητας, μελέτες αξιολογούν μακροπρόθεσμα λειτουργικά αποτελέσματα.

Στόχος: Υγιή νεογνά και βρέφη (Ιδανική Αύξηση και Νευροανάπτυξη)

N. D. Embleton, S. J. Moltu,A. Lapillonne, C. H.P. van den Akker,V. Carnielli, Chr. Fusch, et al, Enteral Nutrition in Preterm Infants (2022): A Position Paper From the ESPGHAN Committee on Nutrition and Invited Experts. JPGN • Volume 76, No 2, February 2023

2022 ENTERAL NUTRITION IN PRETERM INFANTS: ESPGHAN POSITION PAPER

Διατροφικές ανάγκες του προώρου

EMBA Working Group /ESPGHAN/AAP Joint Meeting Consensus on HM Fortification summarizes latest recommended intakes

Συστάσεις

Ανάγκες ενεργειακές, πρωτεϊνικές

TABLE 3 | Recommended enteral protein and energy intakes for clinically stable very low birthweight infants (50, 52, 53).

	Munich consensus 2014	ESPGHAN 2010	Ziegler et al.
Energy (kcal/kg/d)	110–130	110–135	105-127
Protein (g/kg/d)	3.5–4.5	4.0–4.5 (<1 kg) 3.5–4.0 (1–1.8 kg)	3.9-4.0
Protein/Energy (g/100 kcal)	3.2–4.1	3.2–4.1	3.1–3.8
Lipids (g/kg/d)	4.8–6.6	4.8–6.6	–
Carbohydrates (g/kg/d)	11.6–13.2	11.6–13.2	–

TABLE 1. - ESPGHAN CoN recommendations for enteral nutrient intakes

	ESPGHAN 2010 recommendation	ESPGHAN 2022 recommendation
Fluid, mL/kg/d	135–200	**150–180 (135–200)**
Energy, kcal/kg/d	110–135	**115–140 (–160)**
Protein, g/kg/d	3.5–4.5	**3.5–4.0 (–4.5)**
Fat, g/kg/d	4.8–6.6	**4.8–8.1**
Linoleic acid, mg/kg/d	385–1540	**385–1540**
α-Linolenic acid, mg/kg/d	>55	**≥55**
DHA, mg/kg/d	12–30	**30–65**
ARA, mg/kg/d	18–42	**30–100**
EPA, mg/kg/d	–	**<20**
Carbohydrate, g/kg/d	11.6–13.2	**11–15 (–17)**
Sodium, mmol/kg/d	3.0–5.0	**3.0–5.0 (–8.0)**
Chloride, mmol/kg/d	3.0–5.0	**3.0–5.0 (–8.0)**
Potassium, mmol/kg/d	1.7–3.4	**2.3–4.6**
Calcium, mmol/kg/d	3.0–3.5	**3.0–5.0**
Phosphorus, mmol/kg/d	1.9–2.9	**2.2–3.7**
Magnesium, mmol/kg/d	0.3–0.6	**0.4–0.5**
Iron, mg/kg/d	2–3	**2.0–3.0 (–6.0)**

***Agostoni C, Buonocore G, et al**. ESPGHAN Committee on Nutrition.*
J Pediatr Gastroenterol Nutr. (2010)
***Koletzko B, Poindexter B, Uauy R.** World Rev Nutr Diet. (2014)*
***Arslanoglu S, et al** , Front. Pediatr. 2019*
*Position Paper **ESPGHAN Committee Nutrition**, Invited Experts. JPGN Vol 76, No2, Febr2023*

Ενεργειακές, πρωτεϊνικές ανάγκες
(ESPGHAN) ,
American Academy of Pediatrics (AAP),
EMBA/ESPGHAN/AAP Joint Meeting Consensus
διαφορές μεταξύ προώρων

Arslanoglu S, et al (2019) Front. Pediatr.

TABLE 1 | Requirements for protein and energy; best estimates by factorial and empirical methods (44).

Body weight, g	500–1,000	1,001–1,500	1,501–2,000
Weight gain of fetus, g/kg/d	19.0	17.4	16.4
Protein, g/kg/d	4.0	3.9	3.7
Energy, Kcal/kg/d	106	115	123
Protein/energy, g/100 kcal	3.8	3.4	3.0

TABLE 2 | Requirements for major minerals and electrolytes determined by factorial method, listed by body weight (51).

	500–1,000 g		1,001–1,500 g		1,501–2,000 g	
	Accretion	Requirem.	Accretion	Requirem.	Accretion	Requirem.
Ca (mg)	102	184	99	178	96	173
P (mg)	66	126	65	124	63	120
Mg (mg)	2.8	6.9	2.7	6.7	2.5	6.4
Na (meq)	1.54	3.3	1.37	3.0	1.06	2.6
K (meq)	0.78	2.4	0.72	2.3	0.63	2.2
Cl (meq)	1.26	2.8	0.99	2.7	0.74	2.5

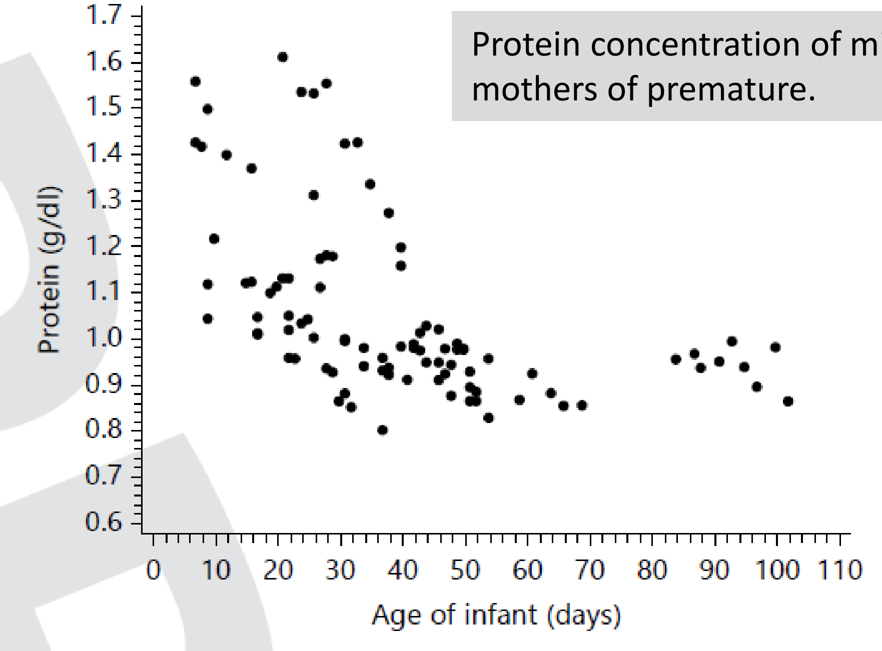
Μείωση πρωτεΐνης μητρικού γάλακτος κατά τη διάρκεια γαλουχίας

Table 1
Macronutrient analysis results (mean ± SD).

Macronutrient	Stage of lactation				P
	0–2 weeks	2–4 weeks	≥4 weeks	DHM (term)	
Protein (g/dL)	1.7 ± 0.3	1.5 ± 0.2	1.3 ± 0.4	1.0 ± 0.1	<0.02 (DHM vs all stages)
Fat (g/dL)	3.0 ± 0.9	3.6 ± 1.1	3.8 ± 0.9	2.5 ± 0.3	≤0.015 (DHM vs 0–2 weeks and ≥4 weeks)
Lactose (g/dL)	6.5 ± 0.5	6.6 ± 0.3	6.5 ± 0.2	6.1 ± 0.4	<0.005 (DHM vs all stages)
Energy (kcal/oz)	17.2 ± 2.4	18.6 ± 2.9	18.9 ± 2.6	14.6 ± 1.4	0.021 (DHM vs 0–2 weeks and ≥4 weeks)

DHM, donor human milk.

1. Επάρκεια θερμίδων
2. Επάρκεια πρωτεΐνης (1st w full feeds volumes)
3. Επάρκεια calcium/ phosphorus



Protein concentration of milk by mothers of premature.

Seminars in Fetal & Neonatal Medicine 22 (2017)
Macedo et al. Maternal Health, Neonatology, and Perinatology (2018)
World Rev Nutr Diet. Basel, Karger, 2014

Ανάγκες πρωτεΐνης και θερμίδων
Μητρικό γάλα με και χωρίς εμπλουτισμό

Fig. 1. Preterm human milk protein content during 12 weeks of lactation and fortification [33].

Seminars in Fetal & Neonatal Medicine (2017)

Table 1: Enteral protein and energy requirements of a 1 kg preterm infant compared to the nutritional content of unfortified and fortified mature human milk

Enteral protein and energy requirements				Nutritional content					
				Human milk, unfortified (11)			Human milk, standard fortified (1 g FM85/20 ml milk) (11,17)		
				Milk volume (ml)			Milk volume (ml)		
Nutrient	Unit	AAP (14)	ESPGHAN (15)	150	180	200	150	180	200
Protein (g/day)		3.4 to 4.2	3.5 to 4.0	1.4 to 1.8	1.6 to 2.2	1.8 to 2.4	2.9 to 3.3	3.4 to 4.0	3.8 to 4.4
Energy	kcal/day	110 to 130	110 to 135	98 to 105	117 to 126	130 to 140	124 to 131	149 to 158	165 to 175
	kJ/day*	462 to 546	462 to 567	412 to 441	491 to 529	546 to 588	521 to 550	626 to 664	693 to 735
Protein:energy ratio	g/100 kcal	2.6 to 3.8	3.2 to 3.6	1.3** to 1.8*** (1.6****)			2.2** to 2.7*** (2.4****)		
	g/100 kJ	0.6 to 0.9	0.8 to 1.0	0.3** to 0.4*** (0.37****)			0.5** to 0.6*** (0.6****)		

South African Journal of Clinical Nutrition 2016; 29(4):157–164

Breastfeeding is best, but «not good enough» for preterm

- Advantages of breast milk, in preterm
- Nutritional requirements to achieve optimum growth?
- Growth not just body weight, but linear growth and head circumference

*Eidelman AI. Breastfeeding and the use of human milk: an analysis of the American Academy of Pediatrics 2012, **AAP, Breastfeeding Policy Statement**. Breastfeeding Med 2012;7:323e4.*

Επιστημονικά δεδομένα (evidence based) για ενίσχυση ΜΓ

Placental transfer of nutrients create **stores** for postnatal period.

Human milk: “preventive therapeutic drug,” **not provide,** fed at usual volumes.

High and **variable nutrient** of preterm during hospitalization.

Insufficient nutrient → **risk of impaired neurodevelopment**.

To **prevent EUGR**, (poor neurocognitive outcome), and deficiencies, **fortification necessary**

Ασφαλής μέθοδος εντερικής σίτισης μητρικό γάλα

Προσθήκη ενισχυτικού

- **μεμονωμένα** μακροθρεπτικά ή μικροθρεπτικά (υδατάνθρακες, λίπος, πρωτεΐνη, ασβέστιο, φώσφορο)
- ενισχυτικό μητρικού γάλακτος βόειας προέλευσης (Bovine MBF) ή ανθρώπινου γάλακτος (Human MBF)

Koletzko B, Poindexter B, Uauy R (eds): Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2014

Key nutrient is protein.

Caloric density, low volumes. **Powder** fortifiers: 1.0–1.1 g protein/dl milk.

Liquid fortifiers (**bovine**):1.0–1.8 g protein/dl, (**Human milk-based**): 0.6 -1.5 g/dl protein at 80-100kcal/dl

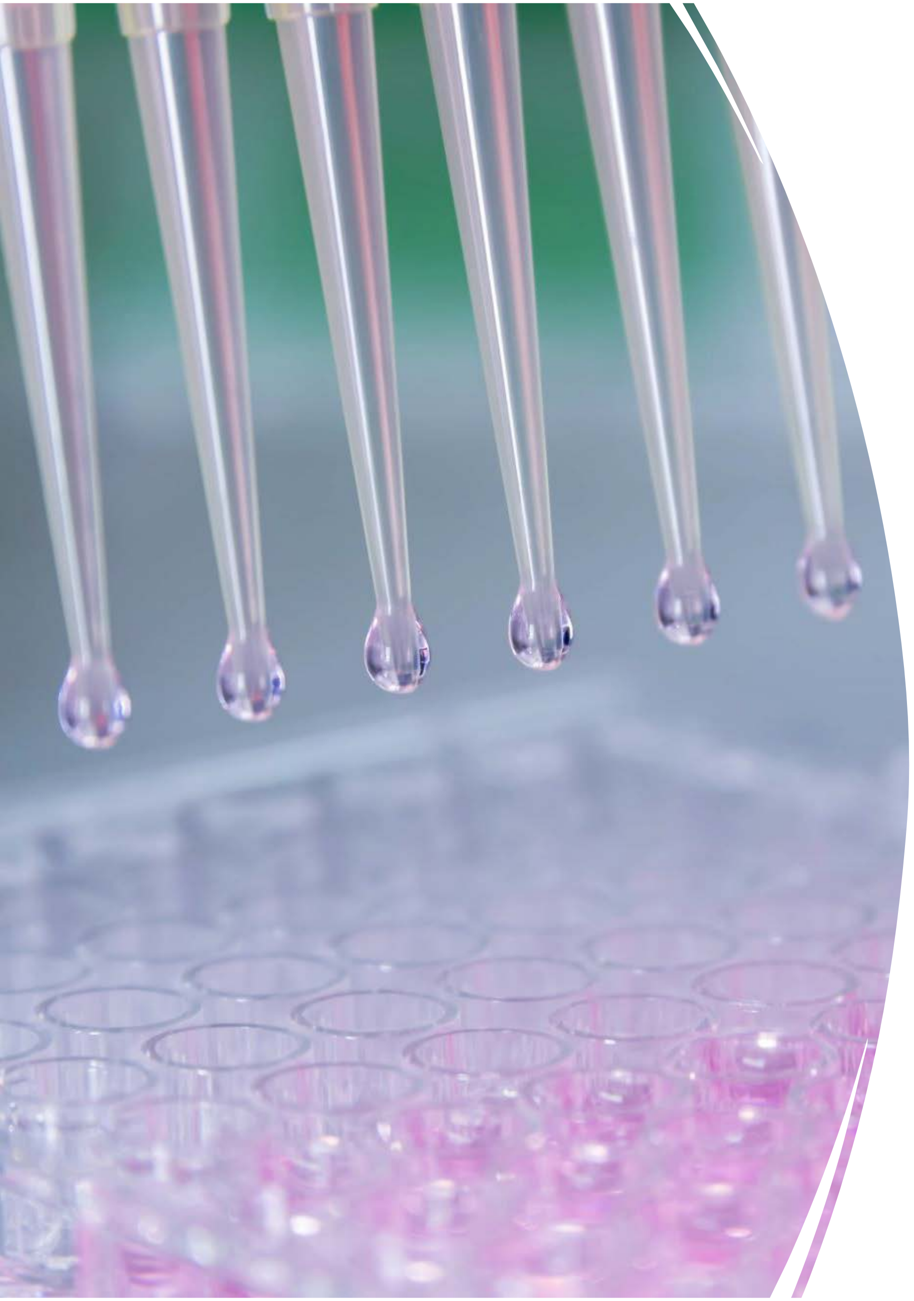
Μέθοδοι ενίσχυσης –εμπλουτισμού μητρικού γάλακτος

1) Προκαθορισμένος (Standard) εμπλουτισμός:

με βάση προκαθορισμένες ανάγκες

προστίθεται πρωτεΐνη, ασβέστιο, φώσφορος και άλλα

1-1.5 g/dL protein, 0 - 1 g/dL fat, 0.4-3.4 g/dL carbohydrates



Μέθοδοι ενίσχυσης –εμπλουτισμού του μητρικού γάλακτος
Adjustable (ADJ) Fortification

2) **Ρυθμιζόμενη ενίσχυση- εμπλουτισμός (individualized adjusted):**

- πρωτεΐνη ανάλογα με δυνατότητα μεταβολισμού
- Δείκτης ουρία (BUN)- Critical levels BUN <9 mg/dL >14 mg/dL
- Avoid protein undernutition and overnutrition.

Arslanoglu S, Bertino E, Coscia A, Tonetto P, Giuliani F, Moro GE. Update of adjustable fortification regimen for preterm infants: a new protocol. J Biol Regul Homeost Agents.(2012) 26(3 Suppl.):65–7.

Μέθοδοι ενίσχυσης –εμπλουτισμού του μητρικού γάλακτος
Targeted fortification

3) **Στοχευμένη ενίσχυση εμπλουτισμός (individualized targeted):**

Αναλυτής (Milk analyzers) πρωτεΐνη- υδατάνθρακες, λίπος, θερμίδες.

Expensive device, requiring calibration

Fusch G, Kwan C, Kotrri G, Fusch C. "Bed Side" human milk analysis in the neonatal intensive care unit: a systematic review. Clin Perinatol. (2017)

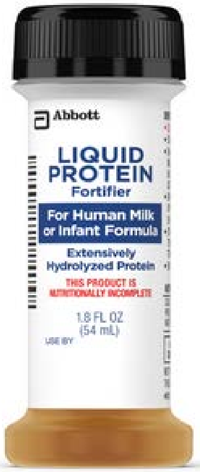
McLeod G, Sherriff J, Hartmann PE, Nathan E, Geddes D, Simmer K. Comparing different methods of human breast milk fortification using measured v. assumed macronutrient composition to target reference growth: a randomised controlled trial. Br J Nutr. (2016)

Συστατικά που περιέχονται:

*Partially Hydrolyzed Whey **Protein** Concentrate, **Maltodextrin**, **Medium Chain Triglycerides**, Low Erucic Canola Oil, **Calcium** Glycerophosphate, Calcium **Phosphate**, **Fish Oil**, Vitamin C, Magnesium Chloride, Calcium Chloride, Sodium Citrate, Choline Bitartrate, Sodium Chloride, Ferrous Sulfate, Vitamin E, Inositol, L-carnitine, Zinc Sulfate, Taurine, Nicotinamide, Calcium Pantothenate, Vitamin A, Riboflavin, Thiamin, Copper Sulfate, Vitamin B6, Folic Acid, Potassium Iodide, Manganese Sulfate, Citric Acid, Vitamin K, Sodium Selenite, Vitamin D, Biotin, Vitamin B12.*

Nutrient	Unit	per 100g powder	per 100kcal	per 4g powder (4 levelled scoops)	per sachet (1g powder)
Energy	kcal	431	100	17	4,25
Protein	g	32,5	7,5	1,3	0,33
Carbohydrate	g	37,1	8,6	1,5	0,38
Sugars	g	1,9	0,4	0,1	0,03
Fat	g	17,5	4,1	0,7	0,18
Linoleic acid	mg	320	62,6	10,8	3,23
Alpha linolenic acid	mg	50	10,6	1,8	0,55
DHA	mg	120	28,8	5	1,25
ARA	mg	120	28,9	5	1,25
Sodium	mg	824	191	33	8,25
Potassium	mg	575	133	23	5,75
Chloride	mg	625	145	25	6,25
Calcium	mg	1734	402	70	17,50
Phosphorus	mg	949	220	38	9,50
Magnesium	mg	125	29	5	1,25
Iron	mg	<0,5	<0,12	≤0,02	0,01
Zinc	mg	15	3,5	0,6	0,15
Copper	µg	1000	238	41	10,25
Manganese	µg	163	38	7	1,75

Nutrient	Unit	per 100g powder	per 100kcal	per 4g powder (4 levelled scoops)	per sachet (1g powder)
Fluoride	µg	<213	<49	<8,5	<2,13
Molybdenum	µg	<60	<14	<2,4	<0,6
Selenium	µg	44	10	1,8	0,45
Chromium	µg	<38	<8,9	<1,5	<0,38
Iodine	µg	280	65	11	2,75
Vitamin A	µg RE	5797	1345	232	58
Vitamin D	µg	138	32	5,54	1,39
Vitamin E	mg αTE	65	15	2,6	0,65
Vitamin K	µg	409	95	16	4
Thiamin (Vitamin B1)	µg	3400	780	130	32,50
Riboflavin (Vitamin B2)	µg	4300	1000	170	42,50
Niacin (Vitamin B3)	mg	57	13	2,3	0,58
Pant. Acid (Vitamin B5)	µg	19000	4300	750	187,50
Vitamin B6	µg	2700	640	110	27,5
Folate	µg	1250	290	50,1	12,53
Vitamin B12	µg	5	1,2	0,2	0,05
Biotin	µg	62	14	2,5	0,63
Vitamin C	mg	297	69	12	3
Choline	mg	19	4,5	0,78	0,20



Βόιας προέλευσης HMF

Cows' milk

Not identical

- ✓ Powders/Liquids
- ✓ Different calories, proteins, pH and composition

Human milk derived human milk fortifiers

Prolact+4 H²MF® Human Milk Fortifier (Human, Pasteurized) Volume = 10 mL Adds at least 4 kcal/fl oz	**Prolact+4 H²MF®** Human Milk Fortifier (Human, Pasteurized) Volume = 20 mL Adds at least 4 kcal/fl oz	**Prolact+6 H²MF®** Human Milk Fortifier (Human, Pasteurized) Volume = 15 mL Adds at least 6 kcal/fl oz	**Prolact+6 H²MF®** Human Milk Fortifier (Human, Pasteurized) Volume = 30 mL Adds at least 6 kcal/fl oz	**Prolact+8 H²MF®** Human Milk Fortifier (Human, Pasteurized) Volume = 40 mL Adds at least 8 kcal/fl oz	**Prolact+10 H²MF®** Human Milk Fortifier (Human, Pasteurized) Volume = 50 mL Adds at least 10 kcal/fl oz
Fortifies human milk to deliver 82 kcal and 2.5 g of protein in 100 mL of nutrition[*,1]	Fortifies human milk to deliver 82 kcal and 2.5 g of protein in 100 mL of nutrition[*,1]	Fortifies human milk to deliver 90 kcal and 2.9 g of protein in 100 mL of nutrition[*,1]	Fortifies human milk to deliver 90 kcal and 2.9 g of protein in 100 mL of nutrition[*,1]	Fortifies human milk to deliver 98 kcal and 3.4 g of protein in 100 mL of nutrition[*,1]	Fortifies human milk to deliver 105 kcal and 3.8 g of protein in 100 mL of nutrition[*,1]

- Human milk
- Not identical, Liquids, Different calories and protein concentrations

Ποια δεδομένα για την αποτελεσματικότητα και την ασφάλεια;

Randomized trials of fortification vs no fortification with Bovine Fortifiers

Not isoenergetic/isoproteinic, blinded

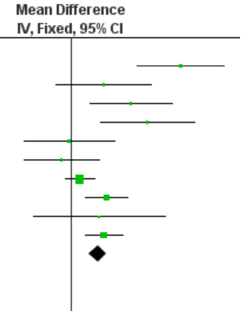
- **Growth better** (weight and head circumference)
- No evidence of **adverse impacts**, (NEC or GI complications)
- Αποδείξεις για την αποτελεσματικότητα και την ασφάλεια

Amissah EA, BrownJ, HardingJE. Protein supplementation of human milk for promoting growth in preterm infants. ***Cochrane Database of Systematic Reviews 2020***

Weight gain

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.1.1 All trials									
Modanlou 1986	26.7	3.4	8	19.4	2.7	10	4.0%	7.30 [4.41, 10.19]	1986
Gross 1987 (1)	19.9	2.5	10	17.7	4.4	10	3.4%	2.20 [-0.94, 5.34]	1987
Gross 1987 (2)	21.5	3.5	17	17.5	3.3	9	4.6%	4.00 [1.28, 6.72]	1987
Polberger 1989	20.4	2.8	7	15.3	3.2	7	3.4%	5.10 [1.95, 8.25]	1989
Pettifor 1989	16.7	5	29	16.8	6.4	28	3.8%	-0.10 [-3.09, 2.89]	1989
Porcelli 1992	11.4	2.7	10	12	3	10	5.4%	-0.60 [-3.10, 1.90]	1992
Lucas 1996	15.6	4.7	137	15	3.5	138	35.2%	0.60 [-0.38, 1.58]	1996
Wauben 1998	16.6	1.6	12	14.2	2	13	16.9%	2.40 [0.99, 3.81]	1998
Nicholl 1999	15.1	3.3	13	13.2	6.4	10	1.8%	1.90 [-2.45, 6.25]	1999
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	21.5%	2.20 [0.95, 3.45]	2007
Subtotal (95% CI)			**325**			**310**	**100.0%**	**1.81 [1.23, 2.40]**	

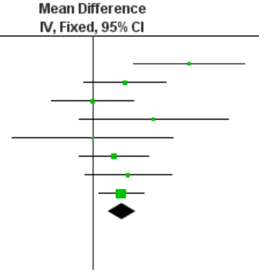
Heterogeneity: Chi² = 32.63, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 6.12 (P < 0.00001)



Head Growth

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.3.1 All trials									
Modanlou 1986	1.09	0.07	8	0.82	0.24	10	6.2%	0.27 [0.11, 0.43]	1986
Gross 1987 (1)	0.92	0.09	10	0.83	0.16	10	11.7%	0.09 [-0.02, 0.20]	1987
Gross 1987 (2)	0.84	0.21	17	0.84	0.09	9	11.3%	0.00 [-0.12, 0.12]	1987
Polberger 1989	1.11	0.13	7	0.94	0.25	7	3.5%	0.17 [-0.04, 0.38]	1989
Porcelli 1992	0.7	0.3	10	0.7	0.2	10	3.0%	0.00 [-0.22, 0.22]	1992
Lucas 1996	1.01	0.47	137	0.95	0.35	138	15.7%	0.06 [-0.04, 0.16]	1996
Wauben 1998	1	0.1	12	0.9	0.2	13	10.1%	0.10 [-0.02, 0.22]	1998
Mukhopadhyay 2007	0.83	0.2	82	0.75	0.2	75	38.6%	0.08 [0.02, 0.14]	2007
Subtotal (95% CI)			**283**			**272**	**100.0%**	**0.08 [0.04, 0.12]**	

Heterogeneity: Chi² = 8.96, df = 7 (P = 0.26); I² = 22%
Test for overall effect: Z = 4.21 (P < 0.0001)



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[Intervention Review]

Multi-nutrient fortification of human milk for preterm infants

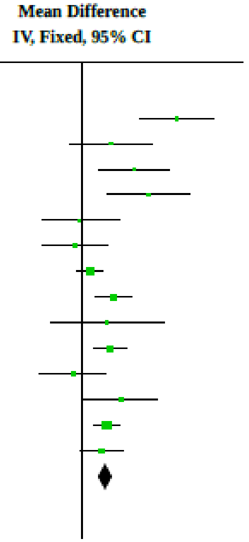
Jennifer Valeska Elli Brown[1], Luling Lin[2], Nicholas D Embleton[3], Jane E Harding[2], William McGuire[4]

Database of Systematic Reviews 2020, Issue 6. Art. No.: CD000343.

Figure 3. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.1 Weight gain (g/kg/d).

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 All trials								
Modanlou 1986	26.7	3.4	8	19.4	2.7	10	2.5%	7.30 [4.41 , 10.19]
Gross 1987 (1)	19.9	2.5	10	17.7	4.4	10	2.1%	2.20 [-0.94 , 5.34]
Gross 1987 (2)	21.5	3.5	17	17.5	3.3	9	2.8%	4.00 [1.28 , 6.72]
Polberger 1989	20.4	2.8	7	15.3	3.2	7	2.1%	5.10 [1.95 , 8.25]
Pettifor 1989	16.7	5	29	16.8	6.4	28	2.4%	-0.10 [-3.09 , 2.89]
Porcelli 1992	11.4	2.7	10	12	3	10	3.4%	-0.60 [-3.10 , 1.90]
Lucas 1996	15.6	4.7	137	15	3.5	138	21.9%	0.60 [-0.38 , 1.58]
Wauben 1998	16.6	1.6	12	14.2	2	13	10.5%	2.40 [0.99 , 3.81]
Nicholl 1999	15.1	3.3	13	13.2	6.4	10	1.1%	1.90 [-2.45 , 6.25]
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	13.4%	2.20 [0.95 , 3.45]
Einloft 2015	19.2	4.3	19	19.9	3.7	19	3.2%	-0.70 [-3.25 , 1.85]
El Sakka 2016	16.8	5.5	25	13.8	4.7	25	2.6%	3.00 [0.16 , 5.84]
Gupta 2018	18	2.9	75	16.1	2.9	73	24.1%	1.90 [0.97 , 2.83]
Adhisivam 2019	9.4	2.2	40	7.9	4.8	40	7.9%	1.50 [-0.14 , 3.14]
Subtotal (95% CI)			**484**			**467**	**100.0%**	**1.76 [1.30 , 2.22]**

Heterogeneity: Chi² = 37.16, df = 13 (P = 0.0004); I² = 65%
Test for overall effect: Z = 7.52 (P < 0.00001)



- Modest increases in **growth rates**.
- Insufficient effect on long term growth or neurodevelopment

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[Intervention Review]

Formula versus donor breast milk for feeding preterm or low birth weight infants

Maria Quigley[1], Nicholas D Embleton[2], William McGuire[3]

[1]National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK. [2]Newcastle Neonatal Service, Newcastle Hospitals NHS Foundation Trust and University of Newcastle, Newcastle upon Tyne, UK. [3]Centre for Reviews and Dissemination, University of York, York, UK

Randomized 363 VLBW, **BM bovine fortifier**

NEC (grade ≥1) 11% with formula, 4% DBM

NEC (grade ≥2) 6.6% vs 1.7%

Trang S, et al. Cost-Effectiveness of Supplemental Donor Milk Versus Formula for Very Low Birth Weight Infants. Pediatrics. 2018;141(3).

Fortified HDM than formula →

lower weight gain, longitudinal growth, head circumference

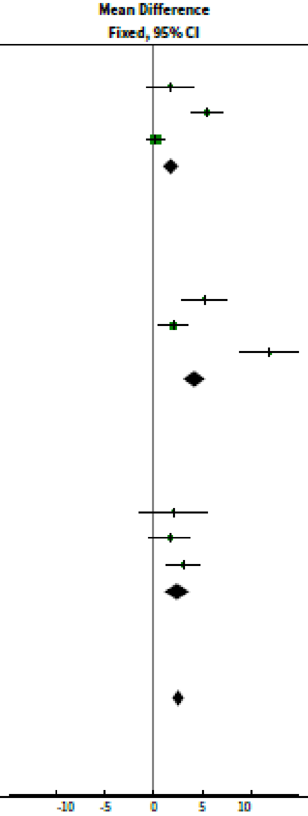
Necrotising Enterocolitis Decreased by DBF

RR with formula 1.9 (95% CI : 1.23, 2.85)

Quigley M, et al. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane database of systematic reviews. 2018;6:CD002971.

Analysis 1.2. Comparison 1 Formula (term or preterm) versus donated breast milk (DBM) (unfortified or fortified), Outcome 2 Weight gain (g/kg/day).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Donor breast milk N	Donor breast milk Mean(SD)	Weight	Mean Difference Fixed, 95% CI
1.2.1 Term formula versus unfortified DBM						
Davies 1977	34	14.7 (4.7)	34	13 (5.4)	5.74%	1.7[-0.71,4.11]
Gross 1983	20	20.4 (2.7)	40	14.9 (3.2)	13.93%	5.5[3.96,7.04]
Raiha 1976	84	13.8 (2.5)	22	13.6 (2)	33.74%	0.2[-0.79,1.19]
Subtotal ***	**138**		**96**		**53.41%**	**1.74[0.96,2.53]**
Heterogeneity: Tau²=0; Chi²=32.04, df=2(P<0.0001); I²=93.76%						
Test for overall effect: Z=4.33(P<0.0001)						
1.2.2 Preterm formula versus unfortified DBM						
Lucas 1984a	30	18 (6)	28	12.8 (2.6)	6%	5.2[2.85,7.55]
Lucas 1984b	56	16.3 (4.5)	59	14.3 (3.1)	16.48%	2[0.58,3.42]
Tyson 1983	42	24.3 (8.2)	34	12.4 (4.8)	3.79%	11.9[8.94,14.86]
Subtotal ***	**128**		**121**		**26.27%**	**4.16[3.04,5.28]**
Heterogeneity: Tau²=0; Chi²=35.94, df=2(P<0.0001); I²=94.43%						
Test for overall effect: Z=7.25(P<0.0001)						
1.2.3 Preterm formula versus fortified DBM						
Cristofalo 2013	24	17 (7.1)	29	15 (5.8)	2.65%	2[-1.54,5.54]
O'Connor 2016	162	25.5 (9.7)	164	23.9 (10)	7.26%	1.6[-0.54,3.74]
Schanler 2005	88	20.1 (6.7)	78	17.1 (5)	10.41%	3[1.21,4.79]
Subtotal ***	**274**		**271**		**20.32%**	**2.37[1.09,3.65]**
Heterogeneity: Tau²=0; Chi²=1.02, df=2(P=0.6); I²=0%						
Test for overall effect: Z=3.63(P=0)						
Total ***	**540**		**488**		**100%**	**2.51[1.93,3.08]**
Heterogeneity: Tau²=0; Chi²=80.95, df=8(P<0.0001); I²=90.12%						
Test for overall effect: Z=8.52(P<0.0001)						
Test for subgroup differences: Chi²=11.95, df=1 (P=0), I²=83.26%						



Favours breast milk

Favours formula milk

When to start?

Start: feeding tolerance
20 mL/kg/d **or** 100 mL/kg/d.

No adverse effects, better nutrition with earlier fortification

Shah SD, et al. Early versus Delayed Human Milk Fortification in VLBW Infants-A Randomized Controlled Trial. The Journal of pediatrics. 2016

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Early fortification of human milk versus late fortification to promote growth in preterm infants. Cochrane Database of Systematic Reviews 2020,

Neonatology

Systematic Review

Neonatology
DOI: 10.1159/000501279

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Early versus Delayed Fortification of Human Milk in Preterm Infants: A Systematic Review

Wesam Alyahya[a] Judith Simpson[b, c] Ada L. Garcia[a] Helen Mactier[d]
Christine A. Edwards[a]

[a]School of Medicine, Dentistry and Nursing, Human Nutrition, University of Glasgow, Glasgow, UK; [b]Neonatal Unit, Royal Hospital for Children, Glasgow, UK; [c]NHS Greater Glasgow and Clyde Human Milk Bank, Queen Elizabeth University Hospital, Glasgow, UK; [d]Neonatal Unit, Princess Royal Maternity Hospital, Glasgow, UK

- No significant impact of EF vs DF on all outcomes.
- Not evidence on optimal time to start fortification.
- Early fortification: 1st feed -20 mL/kg/day
- Delayed fortification: 75ml/kg/day -100ml/kg/day

Human or bovine milk fortifier to fortify breast milk?

- RCT 127 VLBW infants MBM, or donor BM

human to bovine fortifier

No differences in tolerance, or NEC (ROP ΣΣ διαφορά)

- Πολυκεντρική παρατήρησης >1500 νεογνά

Μείωση ΝΕΚ, Θανάτου, Σήψη, ΒΠΔ, ROP

	BOV (n = 768)	HUM (n = 819)	p-Value
NEC (%)	16.7	6.9	<0.00001
Mortality (%)	17.2	13.6	0.04
NEC and/or mortality (%)	28.0	18.2	<0.00001
Weight gain (g/day)	19.5 ± 8.4	20.3 ± 8.6	0.08
Head circumference growth (cm/week)	0.71 ± 0.33	0.69 ± 0.26	0.22
SGA at discharge (%)	48.6	50.3	0.51

Neurodevelopment at 18 Months CA

Bayley, 3rd Edition	Bovine Milk-based Fortifier (n= 50)	Human Milk-based Fortifier (n= 59)	Effect (95% CI)	p value
Cognitive	95.9 (91.7 - 100.0)*	94.7 (90.9 - 98.5)	1.1 (-4.4, 6.5)**	0.70
Language	93.1 (88.0 - 98.2)	92.4 (87.8 - 97.1)	1.2 (-5.1, 7.5)	0.70
Motor	97.7 (93.8 - 101.5)	95.6 (92.0 - 99.2)	1.1 (-4.2, 6.3)	0.69

*Adjusted mean (95% CI). Adjusted using birth weight group (<1000 and 1000-1249 g)
**Adjusted for birth weight group, sex, small for gestational age (y/n), maternal education, below family size-adjusted poverty line (y/n), and any donor milk intake (y/n)

K. Hopperton et al, Nutrient Enrichment of Human Milk with Human and Bovine Milk-Based Fortifiers for Infants Born <1250 g: 18-Month Neurodevelopment Follow-Up of a Randomized Clinical Trial, Curr Dev Nutr. 2019 Dec; 3(12): nzz129.

O'Connor DL, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial. Am J Clin Nutr. 2018;108(1):108-16.

Hair, A. B. et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet. Breastfeed. Med. 11, 70–74 (2016).

*Jensen GB, Ahlsson F, Domellof M, et al. Nordic study on human milk fortification in extremely preterm infants: a randomised controlled trial—**the N-forte trial.*** *BMJ Open 2021*

Active group: human milk-based nutrient fortifier (Humavant +6, Prolacta Bioscience, California, USA).

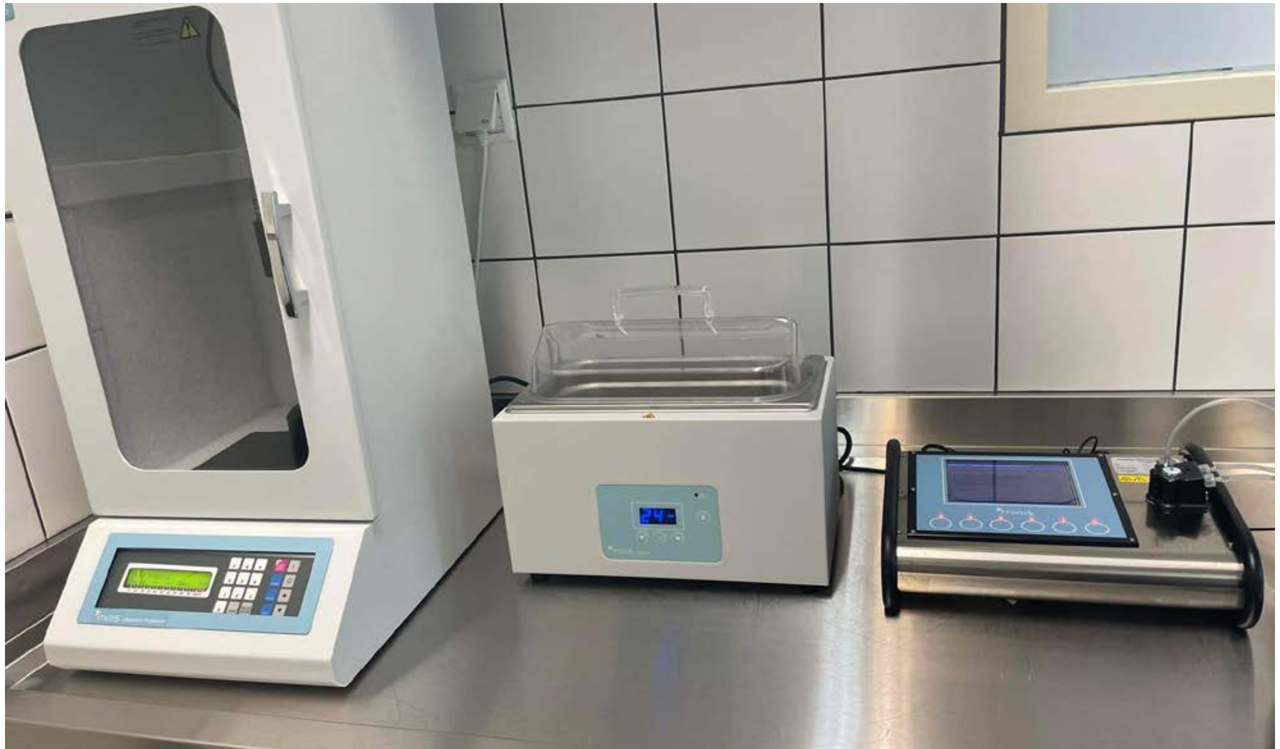
Control group: standard bovine milk-based nutrient fortifier of the particular NICU.

Figure 1 Summary of the N-Forte study actions

	Neonatal period									Follow-up	
Time point	**Birth**	**<100 mL/kg/d**	**7±2 d**	**14±2 d**	**21±2 d**	**28±2 d**	**w34+0**	**w36+0**	**Discharge***	**2 years**	**5.5 years**
Enrolment											
Information given		X									
Eligibility screen		X									
Informed consent		X									
Allocation		X									
Perinatal data	X										
Intervention		◆	—	—	—	—	◆				
Feeding intolerance		◆	—	—	—	—	◆				
NEC, sepsis mortality		◆	—	—	—	—	—	—	◆		
Clinical data noted in the CRF on a daily basis	◆	—	—	—	—	—	—	—	◆		
Neurodevelopmental impairment										X	X
Antibiotics and concomitant medication		X	X	X	X	X	X	X	X		
Weight, length and head circumference**	X		X	X	X	X	X	X	X	X	X
Blood sample			X	X		X	w33+0-6				
Urine sample			X	X	X	X	w33+0-6				
Stool sample			X	X	X	X	w33+0-6				
Breast milk sample			X	X	X	X	w33+0-6				
Adverse events		X	X	X	X	X	X	X	X		

Week (w) refers to postmenstrual week. *Discharge or at latest postmenstrual week 44+0. **Only indicated when measurements must be made in the trial (weight is often measured every day).


ALPINA



Γιατί εξατομικευμένη ενίσχυση;

- Variations in calorie and protein

Διαφορές **μητέρων**, ανάλογα με **ώρα** ημέρας, **γαλουχίας** και **κλάσμα** γάλακτος (πρόσθιο έναντι οπίσθιου γάλακτος -λίπος).

Decreasing variability of maternal milk's macronutrients -**improving growth**

Efficacy and safety of targeted compared standard fortification in VLBW infants

- θερμιδική πυκνότητα, μικρότερους όγκους (γαστρική χωρητικότητα)

Περιορισμός υγρών /περισσότερες θερμίδες (24 και 30 kcal/oz) για αύξηση.

Morlacchi et al. Is targeted fortification of human breast milk an optimal nutrition strategy for preterm infants? An interventional study. J Transl Med (2016)

Gerhard Fusch, Souvik Mitra, Niels Rochow, Christoph Fusch, Target fortification of breast milk: levels of fat, protein or lactose are not related, Acta Pædiatrica, 2015, 104, pp.38–42

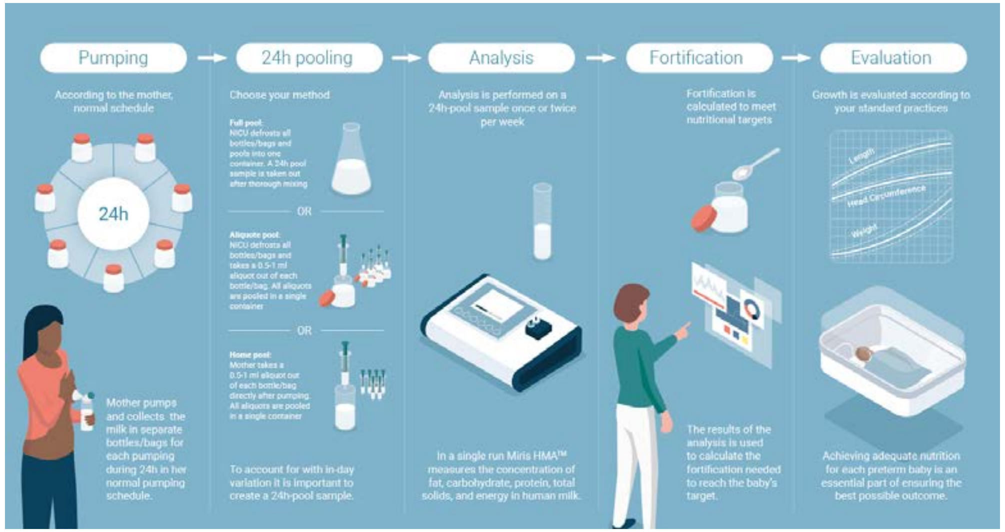
frontiers in Nutrition

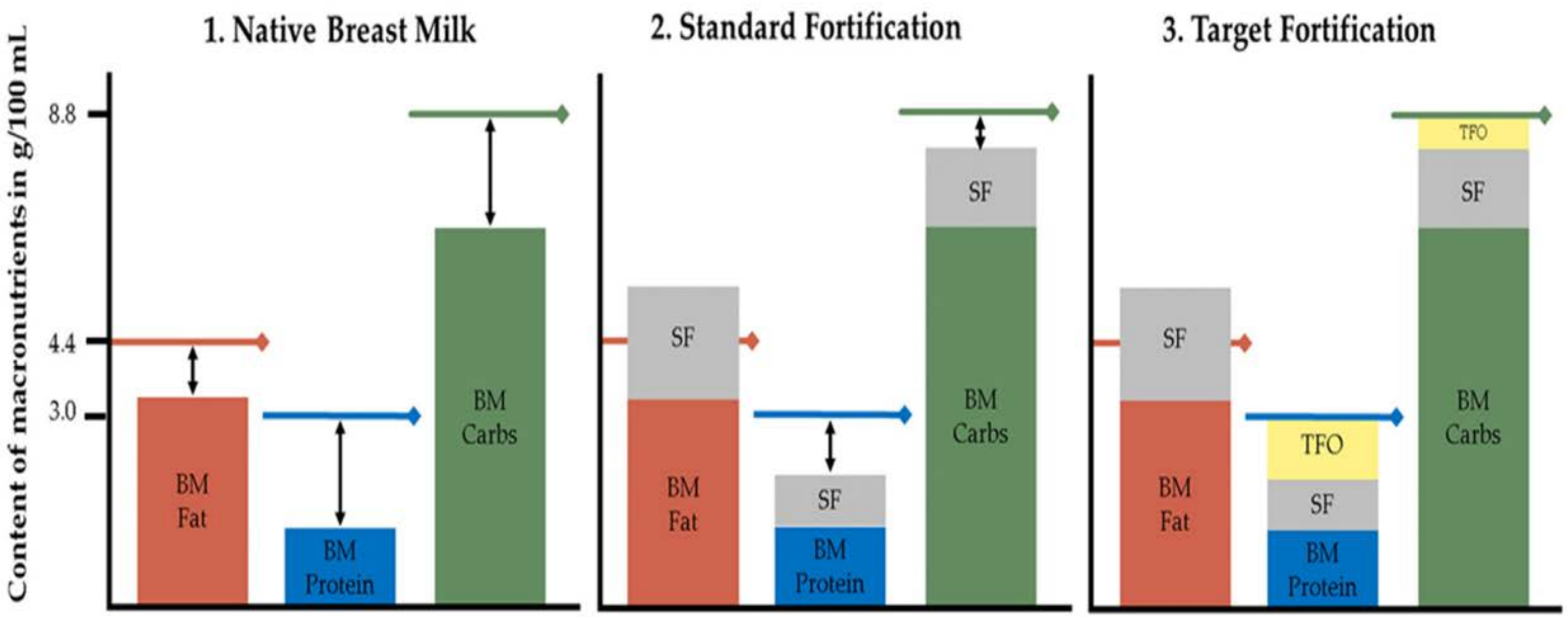
ORIGINAL RESEARCH
published: 21 September 2021
doi: 10.3389/fnut.2021.652641

Check for updates

Individualized Target Fortification of Breast Milk: Optimizing Macronutrient Content Using Different Fortifiers and Approaches

Stephanie Fusch[1,2], Gerhard Fusch[3], Efrah I. Yousuf[3], Markus Rochow[4], Hon Yiu So[5], Christoph Fusch[3,6] and Niels Rochow[3,6,7]*





Morlacchi et al. J Transl Med (2016) 14:195
DOI 10.1186/s12967-016-0957-y

Journal of
Translational Medicine

RESEARCH Open Access

Is targeted fortification of human breast milk an optimal nutrition strategy for preterm infants? An interventional study

Laura Morlacchi[1*], Domenica Mallardi[1], Maria Lorella Giannì[1], Paola Roggero[1], Orsola Amato[1], Pasqua Piemontese[1], Dario Consonni[2] and Fabio Mosca[1]

individualized →more protein, **grew better**

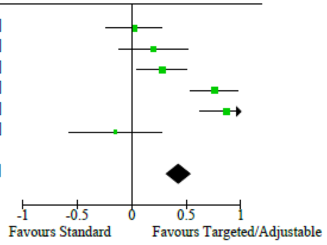
Table 2 Outcomes of the intervention and standardized fortification groups

	Intervention group Mean (95 % CI)	Historical group Mean (95 % CI)	p value
Weekly weight increase (grams)	205.5 (177–233)	155 (132–178)	0.025*
Weekly length increase (cm)	1.6 (1.1–2.2)	1.1 (0.8–1.5)	0.003*
Weekly head circumference increase (cm)	1.0 (0.9–1.1)	0.9 (0.8–1.0)	0.03*
Daily growth velocity (g/kg/day)	15.7 (14.5–16.9)	12.3 (10.7–13.9)	0.005*
Length of stay (days)	51 (42.9–59.1)	45.5 (40.4–50.6)	0.475
Weight at discharge (grams)	2404.3 (2157.9–2650.7)	2085.5 (1911.8–2259.2)	0.07
Length at discharge (cm)	45.9 (44.2–47.6)	44 (43.1–44.9)	0.07
Head circumference at discharge (cm)	32.2 (31.4–33.1)	31.4 (30.6–32.2)	0.161

Analysis 1.2. Comparison 1: Targeted or adjustable vs standard, Outcome 2: Growth velocity, length, mm/d, end of intervention

Study or Subgroup	Targeted/Adjustable Mean	SD	Total	Standard Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Agakidou 2019	1.69	0.48	25	1.67	0.43	23	17.3%	0.02 [-0.24 , 0.28]
Arslanoglu 2006	1.3	0.5	16	1.1	0.4	16	11.6%	0.20 [-0.11 , 0.51]
Hair 2014	1.47	0.47	39	1.19	0.56	39	21.8%	0.28 [0.05 , 0.51]
Kadioglu Simsek 2019	1.71	0.3	20	0.95	0.28	10	24.2%	0.76 [0.54 , 0.98]
Kadioglu Simsek 2019	1.82	0.4	20	0.95	0.28	10	18.8%	0.87 [0.62 , 1.12]
Moro 1995	1.27	0.45	12	1.42	0.61	12	6.2%	-0.15 [-0.58 , 0.28]
Total (95% CI)			**132**			**110**	**100.0%**	**0.43 [0.32 , 0.53]**

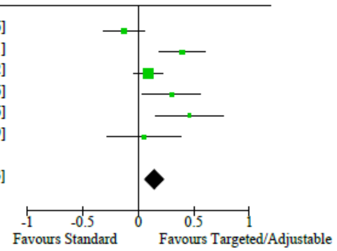
Heterogeneity: $Chi^2 = 41.52$, df = 5 ($P < 0.00001$); $I^2 = 88\%$
Test for overall effect: Z = 7.80 ($P < 0.00001$)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Targeted or adjustable vs standard, Outcome 3: Growth velocity, head circumference, mm/d, end of intervention

Study or Subgroup	Targeted/Adjustable Mean	SD	Total	Standard Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Agakidou 2019	1.48	0.44	25	1.61	0.19	23	19.2%	-0.13 [-0.32 , 0.06]
Arslanoglu 2006	1.4	0.3	16	1	0.3	16	15.9%	0.40 [0.19 , 0.61]
Hair 2014	1.29	0.27	39	1.2	0.31	39	41.3%	0.09 [-0.04 , 0.22]
Kadioglu Simsek 2019	1.09	0.2	20	0.79	0.4	10	10.0%	0.30 [0.04 , 0.56]
Kadioglu Simsek 2019	1.25	0.4	20	0.79	0.4	10	7.5%	0.46 [0.16 , 0.76]
Moro 1995	1.33	0.4	12	1.28	0.44	12	6.1%	0.05 [-0.29 , 0.39]
Total (95% CI)			**132**			**110**	**100.0%**	**0.14 [0.06 , 0.23]**

Heterogeneity: $Chi^2 = 20.37$, df = 5 ($P = 0.001$); $I^2 = 75\%$
Test for overall effect: Z = 3.38 ($P = 0.0007$)
Test for subgroup differences: Not applicable



Moderate- to low-certainty evidence : individualized (targeted or adjustable) increases growth velocity of weight, length, and head circumference compared with standard fortification.
Αποδείξεις μέτριας –χαμηλής βεβαιότητας

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[Intervention Review]

Individualized versus standard diet fortification for growth and development in preterm infants receiving human milk

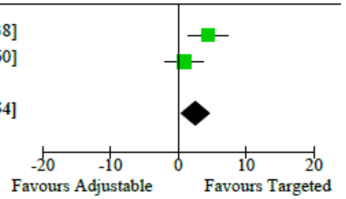
Veronica Fabrizio[1,2], Jennifer M Trzaski[1,2], Elizabeth A Brownell[3,4], Patricia Esposito[1], Shabnam Lainwala[1,2], Mary M Lussier[1], James I Hagadorn[1,2]

Cochrane Database of Systematic Reviews **2020**

Analysis 4.1. Comparison 4: Targeted vs adjustable fortification, Outcome 1: Growth velocity, weight, g/kg/d, end of intervention

Study or Subgroup	Targeted Mean	SD	Total	Adjustable Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bulut 2019	23.1	4.3	16	18.7	4.3	16	47.2%	4.40 [1.42 , 7.38]
Kadioglu Simsek 2019	24.78	5.58	20	24	3.19	20	52.8%	0.78 [-2.04 , 3.60]
Total (95% CI)			**36**			**36**	**100.0%**	**2.49 [0.44 , 4.54]**

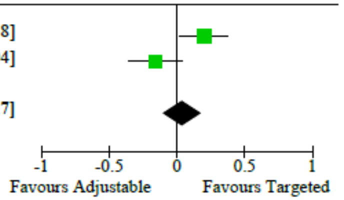
Heterogeneity: $Chi^2 = 2.99$, df = 1 ($P = 0.08$); $I^2 = 67\%$
Test for overall effect: Z = 2.38 ($P = 0.02$)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Targeted vs adjustable fortification, Outcome 3: Growth velocity, head circumference, mm/d, end of intervention

Study or Subgroup	Targeted Mean	SD	Total	Adjustable Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bulut 2019	1.4	0.21	16	1.2	0.3	16	54.4%	0.20 [0.02 , 0.38]
Kadioglu Simsek 2019	1.09	0.2	20	1.25	0.4	20	45.6%	-0.16 [-0.36 , 0.04]
Total (95% CI)			**36**			**36**	**100.0%**	**0.04 [-0.10 , 0.17]**

Heterogeneity: $Chi^2 = 7.05$, df = 1 ($P = 0.008$); $I^2 = 86\%$
Test for overall effect: Z = 0.53 ($P = 0.60$)
Test for subgroup differences: Not applicable



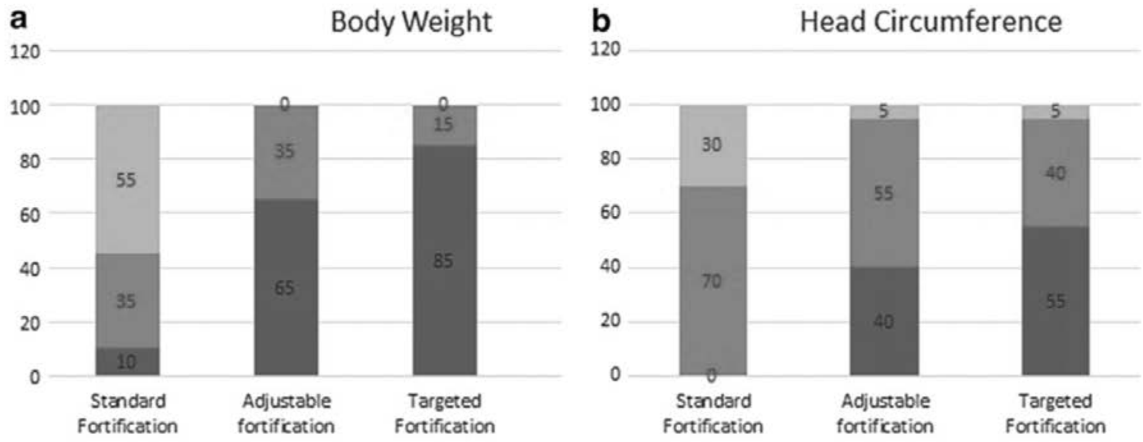
BREASTFEEDING MEDICINE
Volume 14, Number 1, 2019
© Mary Ann Liebert, Inc.
DOI: 10.1089/bfm.2018.0093

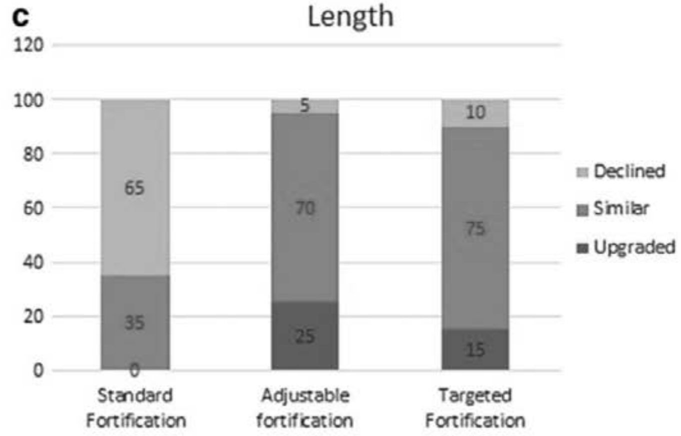
Comparison of the Effect of Three Different Fortification Methods on Growth of Very Low Birth Weight Infants

Gülsüm Kadıoğlu Şimşek, Evrim Alyamaç Dizdar, Sema Arayıcı, Fuat Emre Canpolat, Fatma Nur Sarı, Nurdan Uraş, and Serife Suna Oguz

Συγκρίνοντας τα 3 είδη ενίσχυσης και την εξατομικευμένη με την ρυθμιζόμενη

ADJUSTABLE & TARGETED FORTIFICATION FOR PRETERMS





- Target fortification a little better compared to adjusted fortification.

TABLE 2. GROWTH CHARACTERISTICS OF THE INFANTS

	SF (n=20)	*AF* (n=20)	*TF* (n=20)	p
Daily weight gain [g/(kg·d)]	12 (9–17)	24 (22–26)	25.5 (21–28)	<0.001
HC rate (mm/day)	0.875 (0.5–1)	1.25 (1–1.5)	1 (1–1.25)	<0.001
Length rate (mm/day)	1 (0.75–1.1)	2 (1.5–2)	1.75 (1.5–1.88)	<0.001

Data shown as median (interquartile range).
HC, head circumference.

Clinical Nutrition
Volume 40, Issue 1, January 2021, Pages 54-63

Randomized Control Trials

Individualized target fortification of breast milk with protein, carbohydrates, and fat for preterm infants: A double-blind randomized controlled trial

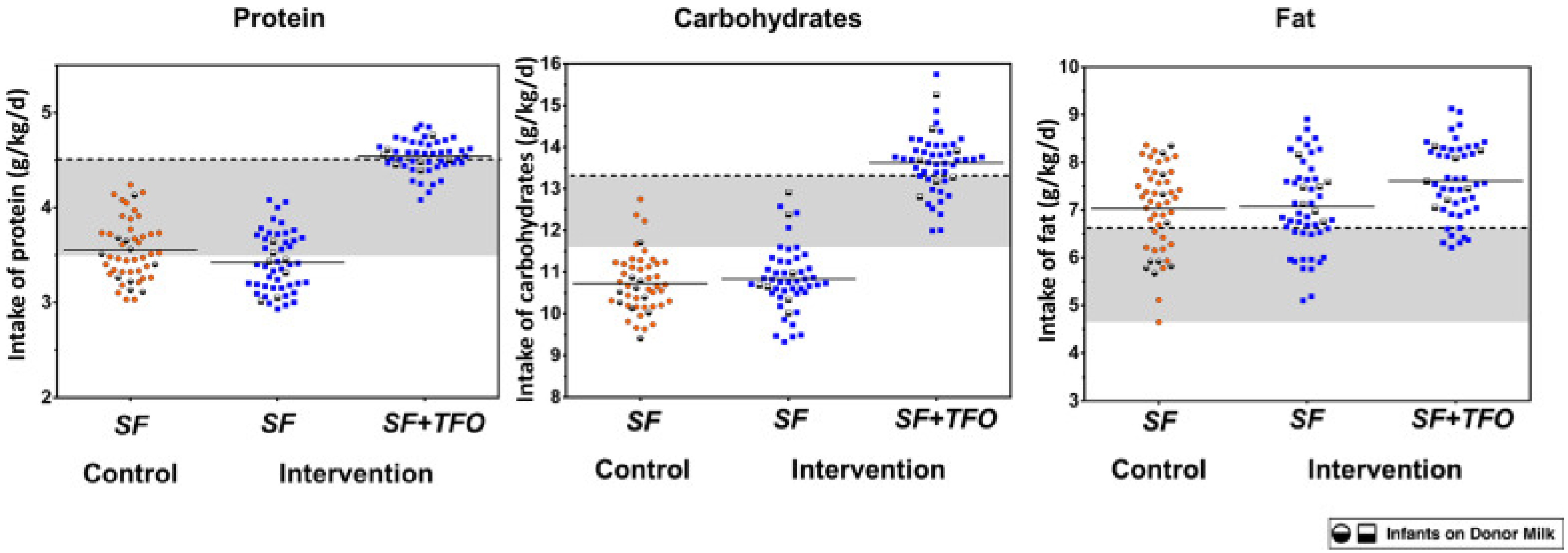
Niels Rochow [a] [b], Gerhard Fusch [a], Anaam Ali [a], Akshdeep Bhatia [a], Hon Yiu So [a], Renata Iskander [a], Lorraine Chessell [a], Salhab el Helou [a], Christoph Fusch [a] [b]

Target Fortification Improves Growth Outcomes

	Control (n=43)	Intervention (n=42)	*P* value
Weight (g)	2280 ± 340	2510 ± 290	0.01
Growth velocity (g/kg/d)	19.4 ± 2.3	21.2 ± 2.3	<0.001
Nutritive efficiency (g/dL)	12.6 ± 1.6	13.9 ± 1.7	<0.001
TFI (mL/kg/d)	155 ± 4	153 ± 4	0.008

$$\text{Nutritive Efficiency} = \frac{\textit{Growth velocity}}{\textit{TFI}}$$

TFO improves growth of preterm infants



Macronutrient intake control group (red) and intervention group before and after TFO (blue).
SF represents intake without target fortification, SF + TFO is intake with target fortification.
Grey shadowed areas show ESPGHAN recommended intakes (SF – standard fortification, TFO – target fortification).

nutrients

MDPI

Article

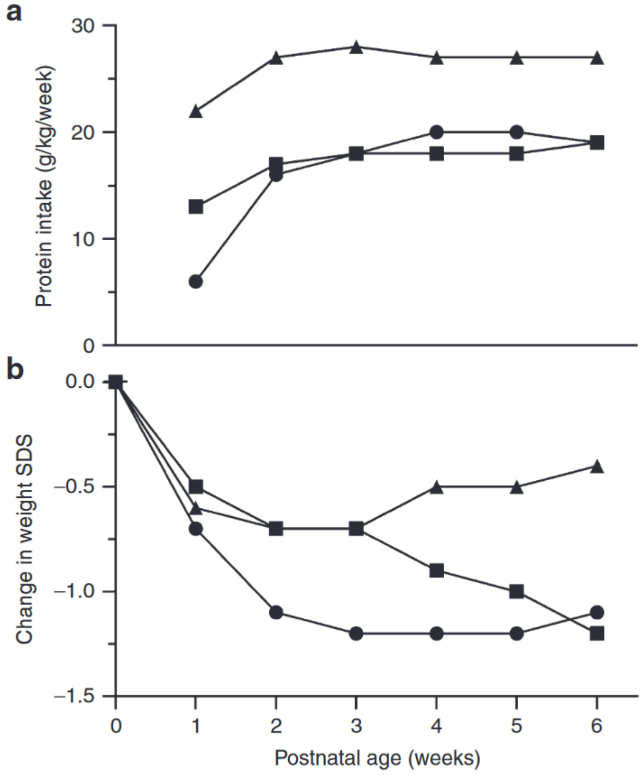
Modifications of Own Mothers' Milk Fortification Protocol Affect Early Plasma IGF-I and Ghrelin Levels in Preterm Infants. A Randomized Clinical Trial

Eleni Agakidou [1,*], Thomais Karagiozoglou-Lampoudi [2], Elisavet Parlapani [1,2], Dimitrios J. Fletouris [3], Kosmas Sarafidis [1], Vasiliki Tzimouli [4], Elisavet Diamanti [1] and Charalampos Agakidis [4]

Modifications of OMM fortification -transient effect on early **plasma IGF-I** and **ghrelin levels** in preterm in a way consistent with the previously recognized **protein-energy/endocrine balance**, programming effect. Individualized fortification preferred mode of feeding.

Changes in IGF-I and ghrelin predisposing to long-term metabolic and cardiovascular disturbances

Ενίσχυση OMM παροδική επίδραση IGF-I και ghrelin συνάδει με ισορροπία πρωτεΐνης -ενέργειας/ενδοκρινών, υποδεικνύοντας αποτέλεσμα προγραμματισμού.



Dietary proteins and IGF I levels in preterm infants

Insulin-like growth factor I(IGF I) play a role in postnatal growth of preterm, have a persisting influence on body composition in childhood.

Pediatric Research Volume 77, 2015

Putet, G.et al, (Early Protein and Obesity in Childhood (EPOCH) study). Br. J. Nutr. **2016**

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[Intervention Review]

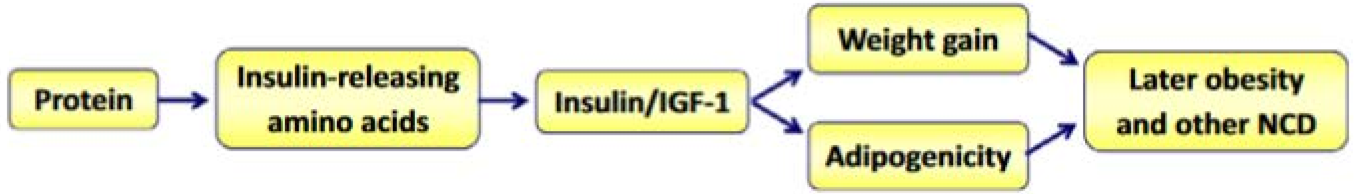
Protein supplementation of human milk for promoting growth in preterm infants

Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD000433

Emma A Amissah[1], Julie Brown[2], Jane E Harding[1]

- Protein to human milk for preterm increase short-term growth.
- Different amounts of protein in multi-component fortifiers, and be designed to determine effects on **length of hospital stay, safety, long-term growth, body fat, obesity, high blood sugar, body composition, cardio-metabolic, and neurodevelopmental outcomes.**

Seminars in Perinatology 43 (2019) 151153



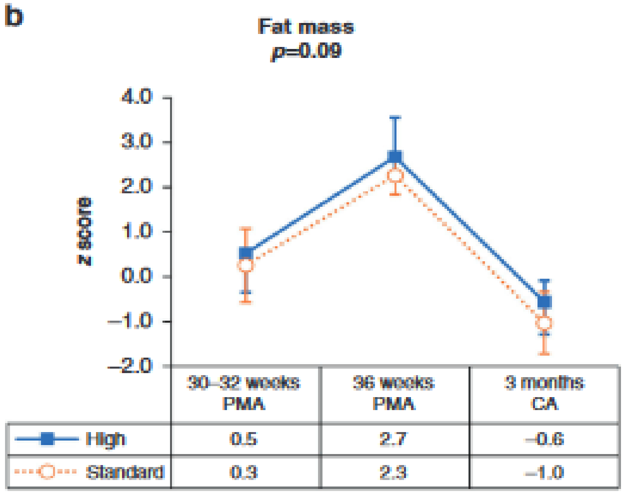
“Early Protein Hypothesis”

CLINICAL RESEARCH ARTICLE

Body composition of extremely preterm infants fed protein-enriched, fortified milk: a randomized trial

Ariel A. Salas[1]✉, Maggie Jerome[2], Amber Finck[1], Jacqueline Razzaghy[1], Paula Chandler-Laney[2] and Waldemar A. Carlo[1]

b



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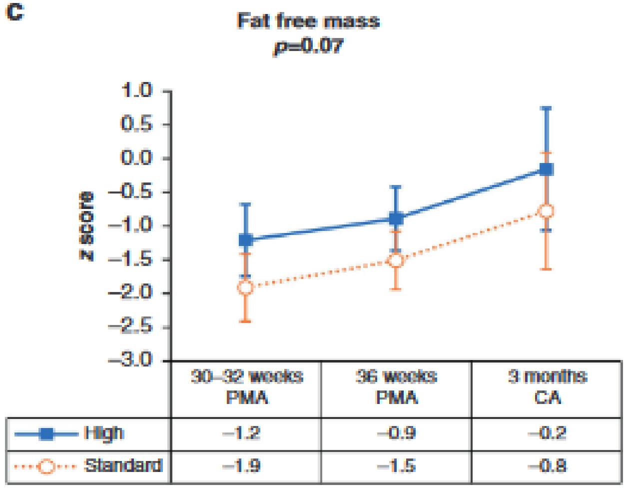

Η αυξημένη εντερική πρόσληψη **πρωτεΐνης** αύξησε τη **μη λιπώδη μάζα** σώματος, το **βάρος** και το **μήκος** σε εξαιρετικά πρόωρα που έλαβαν εμπλουτισμένο σε πρωτεΐνη, ενισχυμένο ανθρώπινο γάλα

Pediatric Research (2022) 91:1231 – 1237

Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA.

nutrients

Article

The Effect of Increasing the Protein Content of Human Milk Fortifier to 1.8 g/100 mL on Growth in Preterm Infants: A Randomised Controlled Trial

Jessica Reid [1], Maria Makrides [1,2], Andrew J. McPhee [1,3], Michael J. Stark [3,4], Jacqueline Miller [1,5] and Carmel T. Collins [1,2,*]

Nutrients **2018**, 10, 634; doi:10.3390/nu10050634

Table 2. Anthropometric changes over the study.

	Intention to Treat Analyses				Per Protocol Analyses [1]			
	High Protein (n = 31)	Standard Protein (n = 29)	Adjusted Mean Difference [2]	p [2]	High Protein (n = 21)	Standard Protein (n = 23)	Adjusted Mean Difference [2]	p [2]
Weight gain (g/week)	245 (230, 260)	258 (244, 272)	−14 (−32, 4)	0.12	245 (228, 262)	262 (247, 277)	−15 (−36, 5)	0.14
Length gain (cm/week)	1.1 (1.1, 1.2)	1.1 (1.1, 1.2)	−0.01 (−0.06, 0.03)	0.45	1.1 (1.1, 1.2)	1.2 (1.1, 1.2)	−0.01 (−0.06, 0.04)	0.62
Head circumference gain (cm/week)	1.1 (1.0, 1.1)	1.1 (1.0,1.1)	0.007 (−0.05, 0.06)	0.79	1.1 (1.1, 1.1)	1.1 (1.1, 1.1)	−0.004 (−0.06, 0.05)	0.88
Weight at study end (g) [3]	2658 (2544, 2771)	2757 (2632, 2883)	−100 (−251, 50)	0.19	2646 (2489, 2805)	2815 (2675, 2955)	−157 (−341, 28)	0.1
Length at study end (cm)	45.2 (44.5, 45.9)	45.8 (45.0, 46.6)	−0.5 (−1.3, 0.3)	0.19	45.2 (44.4, 46.0)	46.3 (45.6, 47)	−0.86 (−1.85, 0.12)	0.09
Head circumference at study end (cm)	33.1 (32.5, 33.6)	33.0 (32.4, 33.7)	0.03 (−0.6, 0.7)	0.92	33.3 (32.7, 33.9)	33.6 (33.0, 34.1)	−0.16 (−0.90, 0.57)	0.66

Data are presented as mean, (95% CI); [1] For inclusion in 'per protocol' analysis, infants must have consumed 70% or more of their trial group HMF; [2] adjusted for sex and gestational age; [3] study end defined as removal of naso-gastric tube or term equivalent, whichever came first.

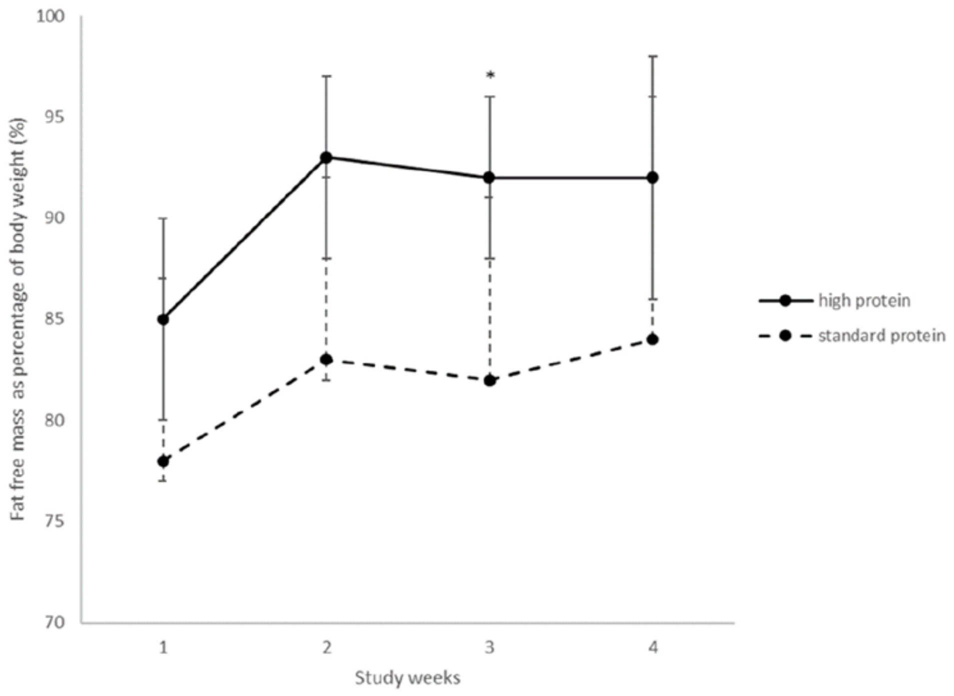

Figure 2. Fat free mass as a proportion of body weight for the first four weeks of the trial. Values are means, error bars are 95% CI. High protein n = 30, 30, 27, 26 and standard protein 29, 27, 26, 23 in weeks 1, 2, 3, 4 respectively. Adjusted for sex and gestational age, group interaction, p = 0.03, time interaction, p = 0.01. group × time interaction p = 0.84; * p = 0.04.

Nutrients 2023, 15, 1533.

Ενισχυμένα HM αύξηση **βάρους, μήκος και κεφαλής** στην έξοδο.
Χαμηλότερο λίπος και περισσότερη **μη λιπώδη μάζα**,
με υψηλότερη πρόσληψης **ενέργειας και λίπους**, και
χαμηλότερη αναλογία **πρωτεΐνης:ενέργεια**.

Article

Individualized Fortification Based on Measured Macronutrient Content of Human Milk Improves Growth and Body Composition in Infants Born Less than 33 Weeks: A Mixed-Cohort Study

Manuela Cardoso [1], Daniel Virella [2,3], Ana Luísa Papoila [2,4], Marta Alves [2,4], Israel Macedo [5], Diana e Silva [6,7] and Luís Pereira-da-Silva [3,8,9,10,*]

Cochrane Central Register of Controlled Trials

Targeted individualized versus standardized preterm human milk fortification-a randomized control trial

Ahuja A, Sikriwal D, Mallaiah R

Journal of pediatric gastroenterology and nutrition, 2022, 74(2), 916- | added to CENTRAL: 31 August 2022 | 2022 Issue 8
https://doi.org/10.1097/MPG.0000000000003446

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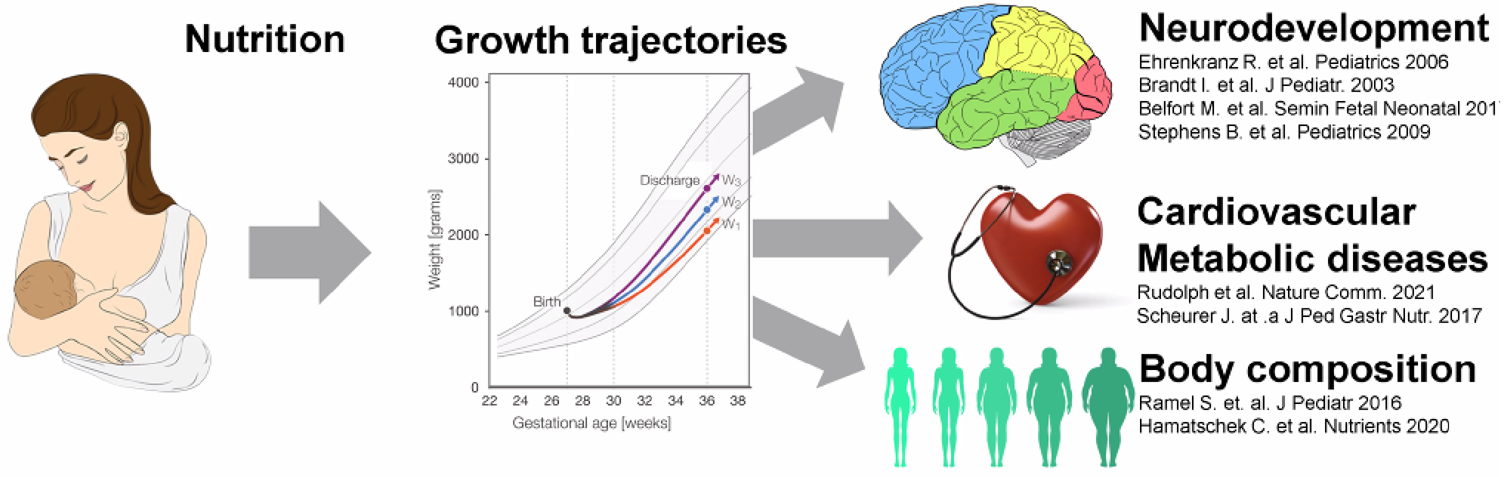
Nutrition and growth is associated with lifelong health



- More **protein** -better body composition growth
- **Quality of weight** gain promoting fat-free mass.
- Fat-free mass: indicator of growth →**neurodevelopment**

Take home message

- ✓ Mother's own milk 1st - Donor HM alternative- risk of NEC (<34 w)
- ✓ Benefits short/long term -(NEC, ROP, BPD sepsis,neurocognitive improvement).
- ✓ Fortify soon (± 50 mL/kg/d) "**Standard Fortification**"
- ✓ "**Individualized Fortification**" to optimize nutrient.
  "**Adjustable**" protein on BUN levels.
  "**Targeted**" on analysis composition
- ✓ Fortifiers to determine effects on **length of hospital stay, safety, long-term growth, body fat, obesity, high blood sugar, body composition, cardio-metabolic, and neurodevelopmental outcomes.**

*Recommendations **E**uropean **S**ociety for **P**ediatric **G**astroenterology **H**epatology and **N**utrition, **A**merican **A**cademy of **P**ediatrics, and Milan **EMBA/ESPGHAN/AAP** Joint Meeting Consensus Arslanoglu S, et al (2019) Front. Pediatr*

Related trials

Targeted individualized versus standardized preterm human milk fortificatio

A Ahuja, D Sikriwal, R Mallaiah

Journal of pediatric gastroenterology and nutrition, **2022**, 74(2), 916- | adde

Does earlier enrichment of human breast milk with nutrients leads to earlie
https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/07/026744, **2020**

Early Routine vs. Selective Human Milk Fortification in Extremely Preterm Ir

https://clinicaltrials.gov/show/NCT04284280, **2020** | added to CENTRAL: 31

Σας ευχαριστώ

A clinical trial to study the effects of adjusted fortification versus standard fo
neonates CTRI/2018/03/012462

https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2018/03/012462, **2018**

Targeted vs Standard Fortification of Breast Milk NCT03775785

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Comparison of Mothers milk with formula against Mothers milk with fortifie

https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2021/10/037446, **2021**