maria Fareri children's Hospital
AT WESTCHESTER MEDICAL CENTER

The origins of the Milky Way and the power of human milk

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Liquid Gold Preemie Milk Bank

"Support the Mothers; Nourish the Babies"

- No conflict of interest
- This talk is intended to provide food for thought

Objectives

- The legend of Hercules, brief review of the evolution of mammalian milk
- The wonderful wallaby milk and stages of human lactation
- Myths and facts about cow milk, infant formula and fortifiers
- AAP on donor human milk
- Brief history of donor human milk banking from antiquity to today
- The pathway of the milk from the donor to the recipient
- The landscape of human milk banking in NYS
- Benefits of donor human milk for preterm neonates
  - Effects on growth
  - Reduction of morbidities
  - Improved lean body mass and brain structure
- Liquid Gold Preemie Milk Bank at MFCH

Rubens, 1637, Museo de Prado, Madrid, Spain

Tintoretto, , 1575, National Gallery, London, UK

Heracles (Hercules)
Zeus,(Jupiter)
Hera (Juno)
Alcamene

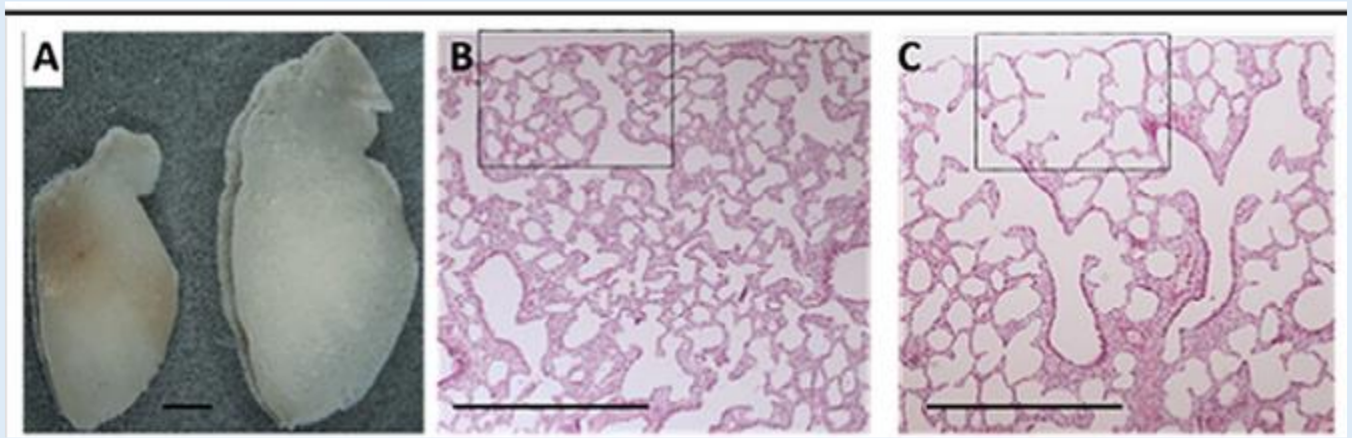
Breastfeeding is 200 million years old

- Prototherians (monotrimes, platupus): egg laying mammals, the young are extremely immature, most of their development is complete after birth
- Metatherians (marsupials, wallaby): live born young, extremely immature, equivalent to 8 weeks human fetus
- Eutherians (placental mammals): various stages of maturity of the young
- All three groups of mammals are characterized by the ability of the female of the species to produce milk by a mammary gland. The milk supplies growth factors and immunological components to young mammals
- Asynchronous concurrent lactation with different content of macronutrients in marsupials

Marsupial and monotreme milk—a review of its nutrient and immune properties. Stannard HJ, Miller RD, Old JM. PeerJ 2020, 8:e9335

The marvelous wallaby breast milk

- Gestation is very short (29 days), lactation is very prolonged (over 300 days)
- Cultured mouse embryonic lung with wallaby milk shows different patterns of growth with branching and alveolar development only when the milk is 40-100 days of lactation
- Cross fostering of newborn wallaby with wallaby mothers producing milk <40 days have smaller and less mature lungs when compared to controls
- Surge of growth factors, hormones and macronutrients between 40 and 100 days



Marsupial and monotreme milk—a review of its nutrient and immune properties. Stannard HJ, Miller RD, Old JM. PeerJ 2020, 8:e9335
Modepalli et all, 2015, 2016

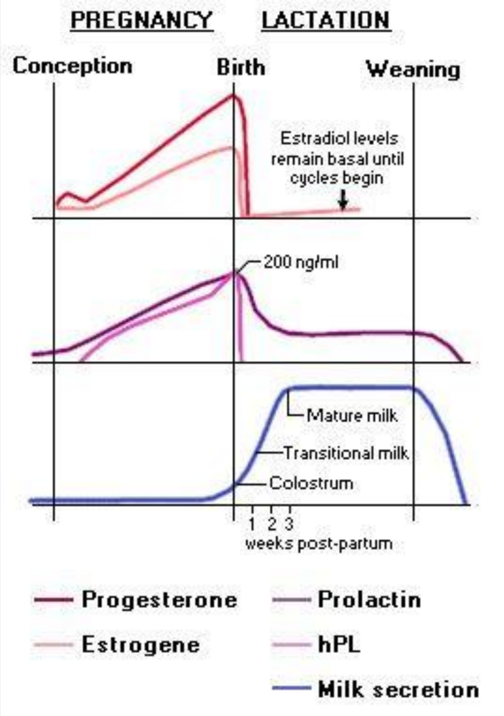
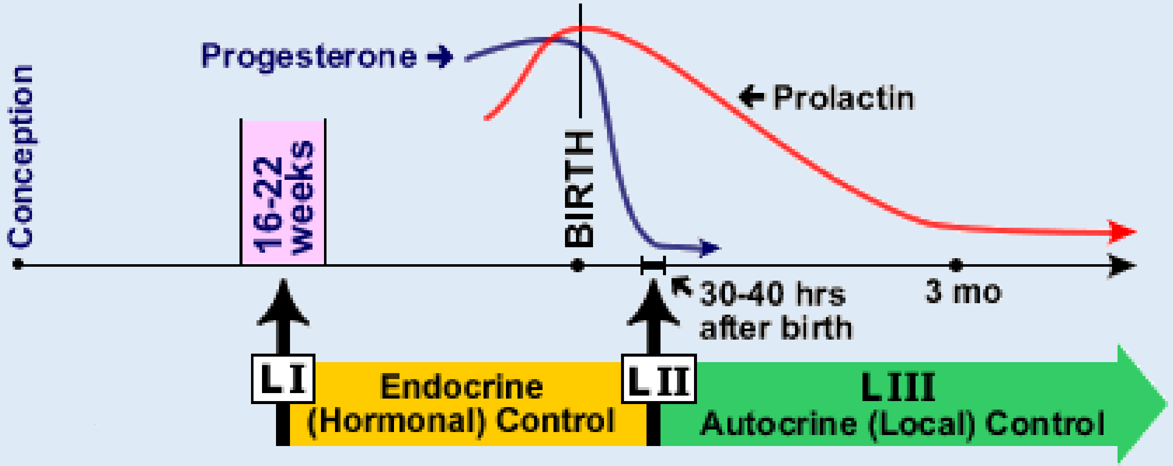


Table 16. Mammogenic, lactogenic and galactopoietic (lactopoietic) hormones

Mammogenic	Lactogenic	Lactopoietic
Estrogens Progesterone Prolactin Growth hormone	Prolactin Insulin Glucocorticoids	Growth hormone Glucocorticoids Thyroid hormones Insulin Parathyroid hormone Prolactin (in goat and ewe)

Mammogenesis = mammary development
Lactogenesis = initiation (onset) of lactation
Lactopoesis = milk secretion (maintenance of lactation)



Human Milk

- Biologic dynamic fluid with great variability in composition
- Duration of gestation: higher whey, fat, immunologic, growth factors with prematurity
- Days after delivery: colostrum, transition, mature milk
- Style of extraction: by the infant, manual, electric pump
- Frequency of extraction
- Within the feeding cycle: higher fat in hind milk
- Maternal ethnicity and BMI: HMO type: fucosilated, acidic, sialic acid, high BMI with lower HMO
- Maternal diet: PUFA and fat content
- Live cells and bacteria: immune development and metabolic programming; stem cells

Bacteriological, biochemical, and immunological properties of colostrum and mature milk from mothers of extremely preterm infants. Moles L. J Pediatr Gastroenterol Nutr. 2015 Jan;60(1):120-6.
The origin of human milk bacteria: is there a bacterial entero-mammary pathway during late pregnancy and lactation? Rodríguez JM . Adv Nutr. 2014 Nov 14;5(6):779-84.
Dominguez-Bello, M.G. *et al. Proc. Natl. Acad. Sci. USA* 107, 11971–11975 (2010).

Antimicrobial factors	Growth factors
secretory IgA, IgM, IgG lactoferrin lysozyme complement C3 leucocytes bifidus factor lipids and fatty acids antiviral mucins, GAGs oligosaccharides	epidermal (EGF) nerve (NGF) insulin-like (IGF) transforming (TGF) Vascular (VEGF) taurine polyamines
Cytokines and anti-inflammatory factors	**Digestive enzymes**
tumour necrosis factor interleukins interferon-g prostaglandins a_1-antichymotrypsin a_1-antitrypsin platelet-activating factor: acetyl hydrolase	amylase bile acid-stimulating esterase bile acid-stimulating lipases lipoprotein lipase proteases elastase
Hormones	**Transporters**
feedback inhibitor of lactation (FIL) insulin prolactin thyroid hormones corticosteroids, ACTH oxytocin calcitonin parathyroid hormone erythropoietin	lactoferrin (Fe) folate binder cobalamin binder IgF binder thyroxine binder corticosteroid binder
Potentially harmful substances	**Others**
viruses (e.g., HIV) aflatoxins trans-fatty acids nicotine, caffeine food allergens PCBs, DDT, dioxins radioisotopes drugs	casomorphins d -sleep peptides nucleotides DNA, miRNA Stem cells WBC

Human Milk Composition: Nutrient and Bioactive Factors. Ballard O. Pediatr Clin North Am 2013

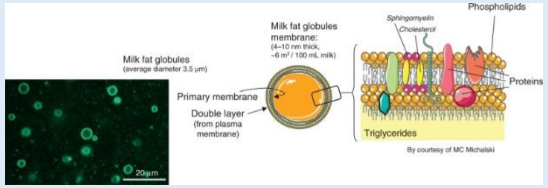
Author (year), n	Protein Mean ± 2SD 100 ml	Fat Mean ±2SD 100 ml	Lactose Mean ±2SD 100 ml	Energy Mean ±2SD 100 ml
Term infants, mature milk, 24 hour collection				
Nommsen (1998), n=58	1.2 (**0.9**-1.5)	3.6 (2.2-5.0)	7.4 (7.2-7.7)	70 (57-83)
Donor Human Milk Samples				
Wojcik (2009), n=415	1.2 (0.7-1.7)	3.2 (1.2-5.2)	7.8 (6.0-9.6)	65 (43-87)
Michaelsen (1990), n=2553	0.9 (0.6-1.4)	3.6 (1.8-8.9)	7.2 (6.4-7.6)	67 (50-115)
Representative values, mature milk, term infants				
Reference standard	**0.9**	**3.5**	**6.7**	**65-70**
Preterm, 24 hour collection, first 8 weeks of life				
Bauer& Gerss (2011) Born < 29 weeks, n=52 Born 32-33 weeks, n=20	 **2.2** (1.3-3.3) 1.9 (1.3-2.5)	 4.4 (2.6-6.2) 4.8 (2.8-6.8)	 7.7 (6.4-8.8) 7.5 (6.5-8.5)	 78 (61-94) 77 (64-89
Preterm Donor Milk				
Hartmann (2011), n=47	**1.4** (0.8-1.9)	**4.2** (2.4-5.9)	**6.7** (5.5-7.9)	70 (53-87)

Ballard,O. Human Milk Composition: Nutrients and Bioactive Factors. Pediatr Clin North Am 2013

Myths and Facts about Human and Bovine Milk

- pH 7.15 vs 6.58
- Less mineral content (Na, Ca), higher lactose
- Total protein: x 4 lower
- Whey to casein ratio:
  - Colostrum 80:20
  - Transition milk 60:40
  - Mature milk 50:50 vs 20:80
- The major whey protein is alpha lactalbumin
  - 41% of the whey; 22% of total protein vs 3%.
  - 30% difference in AA types of human milk whey vs cow milk whey
- No alpha lactoglobulin vs 50% of total protein
- Distinctive predominance of lysine, cysteine and tryptophan
  - Tryptophan is a precursor to serotonin
  - Cysteine is part of the glutathione
  - Cysteine is a precursor to taurine
- Casein contains high proportion of essential amino acids: histidine, methionine, phenylalanine and valine
  - Alpha s1, alpha s1 and kappa vs beta casein

Myths and Facts about Human and Bovine Milk



- Lipids in both human milk and formula are the predominant source of energy
- Fat in formulas is from vegetable sources: palm, coconut, safflower and soy
- >95% of the fat is as triglycerides
- Palmitic acid is the most abundant in human milk and increases with duration of lactation esterified in distinct sn2 position on glycerol, oleic acid is the next most abundant
- Human milk has 34-47% saturated FA, 31-43% monounsaturated FA, 10-35% PUFA
- LA and alpha LA are precursors to LC PUFA
- Formulas have higher LA and ALA
- ARA:DHA are added in formula
- Cholesterol content in human milk is high: bile acids, hormones, Vit. D, lipoproteins
- Nervonic acid, gangliosides, sphingomyelin
- Human milk fat modulate gastrointestinal function, lipoprotein metabolism, cell membrane composition and function, signaling pathways

The Comparison of Nutritional Value of Human Milk with Other Mammals' Milk. Renata Pietrzak-Fie´cko. Nutrients 2020
Fatty Acid Profiles of Various Vegetable Oils… Wai Phyo Aung. Nutrients 2018

Types of Fortifiers

- Enfamil® Human Milk Fortifier Acidified Liquid: hydrolyzed whey, acidic
  - Whey; "fast" protein, anabolic effect
  - Decreases lysozyme activity (Perrin M, Parvez B). New Product, multi-use, neutral pH
- Similac® Human Milk Fortifier Concentrated Liquid: hydrolyzed casein, neutral pH
  - Casein: "slow" protein, anticatabolic
  - Biologically active peptides
- Displacement effect (5 ml/25 ml of milk)
  - Exposure to cow milk proteins
  - Timing of fortification
- Prolacta+ H^2MF®: multi component with intact whey and casein
- Prolacta CR™: 25% cream (Improved weight gain. Hair A. JPeds 2014)
- Liquid Protein Fortifier Abbott Nutrition: dipeptides and AA
- Powder preterm formulas (contamination potential, no studies about the biologic effect on the immunologic breast milk factors))
- Individualized fortification based on weight gain, BUN and acidosis

Radmacher PG, Lewis SL, Adamkin DH. Individualized fortification of human milk using real time analysis. Journal of Neonatal Perinatal Medicine 2013; 6:319-323

Preterm and Transitional Formulas

Indication	Specialty diet
Premature GA <34 weeks BW <1800gm	High Pro, High Vitamin/Minerals, High Ca/Phos Premature Enfamil 20, 22, 24 kcal/oz (40% MCT) **80:40** Whey:Casein Similac Special Care 20, 22, 24 (50% MCT) **60:40** Whey:Casein Contain single HMO DHA and ARA
Premature Transitional GA~34-37 weeks >1800gm From 6 to 12 month CGA	High Pro, High Vitamin/Mineral, 20-25% MCT, Enfamil Enfacare 22 kcal/oz (20% MCT) 80:20 Whey Casein Neosure 22 (25% MCT) 60:40 Whey Casein Contain single HMO DHA and ARA

AAP Recommendations: 2004, 2005, 2012

- Breast milk, appropriately fortified is the most optimal nutrition for the preterm infants. When mothers milk is not available or is in insufficient quantities, pasteurized donor human milk (PDHM) is the best supplement

- Present recommendations are designed to provide nutrients to approximate the rate of growth and composition of a normal fetus of the same postmenstrual age: Weight: 15-20gm/kg/day, HC and length: 1 cm/week

American Academy of Pediatrics, Pediatric Nutrition Handbook, 5th Edition, 2004
AAP 2005, 2012

Early History of Donor Milk Usage

- Practice is ancient and common in many cultures
  - Ancient Romans: Columna Lactaria
  - Jewish: Moses
  - Islamic: Mohammed
  - Imperial China (nai ma)
  - India: Mughal court
  - Wet nurses
  - Hired woman to breast feed and care for another's child
  - The mother is unstable, ill, dies, or is unsuccessful at breastfeeding
  - Wet nursed children may also be referred to as "milk siblings"
  - Wet nurses during slavery

Jones, History of North American Donor Milk Banking: One hundred years of progress, J of Hum Lac;19 (3);2003

History of Donor Milk Banks

- First recorded donor bank in Vienna in 1909, First bank in US (Boston) in 1910 and officially registered as a bank in 1919
- Collection in the early 20th century
  - Daily collection from donor homes, kept chilled on ice
  - 1930's leave sterile containers and pick up daily
  - 1939-Publication of Standards for operating a "directory" (MacPherson and Talbot, 1939)
- 1934: 8000 oz American/Canadian donor milk for the Dionne quintuplets
- 1939 more than 12 North America
- By 1980 there were 56 milk banks in USA. (Stewart's dispensary of donor milk)

Jones, History of North American Donor Milk Banking: One hundred years of progress, J of Hum Lac;19 (3);2003

Fall and Rise Again of Milk Banks

- HIV/AIDS crisis in 1980's resulted in closure of all banks
- Research on pasteurization and benefits of donor milk has lead to a sharp increase of donor milk banks from 1990s:
  - Non profit: 26 in North America, over 200 in the world, hospital based or free standing
  - For profit: Prolacta Bioscience. Medolac, Helping Hands, National Milk Bank, Tiny Treasures, Mothers' Milk Cooperative; Ambrosia
  - Community Peer to Peer Sharing: Eats on Feets, Rose, friends
  - Internet based selling: Only the Breast, Craig's list
    - 10% of samples have bacterial and non-human milk contamination, caffeine and tobacco byproducts
  - FDA advises against milk sharing but the practice is increasing

Jones, History of North American Donor Milk Banking: One hundred years of progress, J of Hum Lac;19 (3);2003
Keim SA. Pediatrics 2013, 2015
Perrin MT. Journal of Human Lactation 2016, Vol. 32(2) 229–237
FDA 2010

Human Milk Banks of North America (HMBANA) www.hmbana.org

- Established 1985
- Non profit organization
  - Main goals to standardize milk banking practices
  - Act as a liaison between member banks and governmental agencies
  - Facilitate communication among member banks
  - Facilitate the establishment of new donor milk banks
  - Provides educational recourses
  - Develops guidelines
- 1990: 1st edition of "Guidelines for Establishment and Operation of Donor Human Milk Bank"
- Cost approximately 3-5 dollars/oz plus shipping
- Donors are not reimbursed
- 7.4 million ounces of donor milk was dispensed in 2019

Regulation of Donor Milk Banks in USA

- FDA regulates donor milk as food and recommends against feeding breast milk acquired directly from individuals or through the Internet (2010 FDA Working Group. Pediatric Advisory Committee)
- Prior to 2000, WIC authorized banked human breast milk
- State Departments of Health & State laws
  - TX – state guidelines related to procurement, processing and distribution of human milk
  - NY, CA, MD – laws requiring banks to be licensed with state as tissue bank before processing and distributing donor milk
- New York State Department of Health: Tissue Resources Program

NYSDOH Licensing

- Licensed Processing Centers (Milk Banks):
  - **WMC Preterm Milk Bank: Opened in 10/2019**
  - The New York Milk Bank: Opened in 2016. 200,000 oz of PDHM dispensed in 2019
  - Crouse Hospital
  - Mothers' Milk Bank Northeast
  - Prolacta Bioscience
  - Medolac
- Distributing Centers: All hospitals, Hudson Valley Breastfeeding
  - 16/18 RPC and many level III NICU, some NB Nurseries in NYS provide donor milk
- Milk Depots for MMBNE and NYMB

Steps to Obtain Donor Milk

- Policies and procedures, donor milk tracking and annual reporting to NYSDH/Tissue Resource Center
- Order or Prescription by a Licensed Prescriber (MD, DO, NP)
- Signed parental consent
- Cost for in-patient use is not prohibitive in NYS:
  - Insurance reimbursement in NYS since 2017 for inpatients (only 6 other states)
  - All infants with GA <34 weeks and BW <1500 g, post NEC and infants with congenital cardiac and GI during the entire NICU stay
  - Most NICU use until 34 weeks CGA
  - Hospitals cover the costs of fortifiers
- $5.00/oz ($0.17/ml) from non profit milk banks
- For profit milk banks (Prolacta Bioscience, Duarte, CA)
  - $32/oz for ready to feed preterm milk: 24, 26, 29 Cal/oz. Vat Pasteurization
  - $167/20 ml Prolact HM+4 (makes 100 ml of milk, 24 cal/oz)
- Lactation support and education should be provided in tandem with donor milk programs

Ensuring the Safety of The Donor Milk

- 4 steps of screening and testing of donors:
  - initial screening interview
  - detailed life style questionnaire
  - medical clearance by the providers of the donor mother and her infant
  - serologic testing: HIV 1&2, HTLV 1&2, HepB, HepC, Syphilis
- Exclusion if any infection risks (e.g. *residence in Europe*, tattoo, partner who has been in jail, blood transfusion within *12* months)
- Confirmation of good health <u>with each deposit</u> and <u>serologic re-screening every 6 months</u>
- Donor education: collection, storage, shipping and transportation of milk
- Additional regulations by NYSDOH which categorizes donor milk as tissue/organ
- Each batch is tested for bacterial growth (0 CFU/ml)

HMBNA 2015 Guidelines for the Establishment and Operation of a Donor Milk Bank
NYSDOH, Wadsworth Center, Blood and Tissue Resource Program

Breast Milk Donors or Sharers

- 91% non-Hispanic white
- 95% married
- 71% college educated
- 57% employed
- Influenced by Healthcare Professionals: Brazilian and US experience of Donor Mothers: 62% vs 14%
- Large number of women share instead of donating to non profit banks due to lack of banks in their geographic area
    - Primary motivator: helping someone, personal connection
- Milk Depot and FedEx shipping

Expanding the supply of pasteurized donor milk: Understanding why peer to peer sharers in US do not donate to Milk Banks Perin MT. J Hum Lactation 2016, 32
Thomac ACP et al. The human milk donation experience: Motives, influencing factors and regular donation. J Hum Lact 2008;24:69–76.
Palmquist AEL, Doehler K. Contextualizing online human milk sharing: structural factors and lactation disparity among middle income women in the U.S. Soc Sci Med. 2014;122:140-147
Osbaldiston R, Mingle LA. Characterization of human milk donors. J Hum Lact. 2007;23(4):350-357.

Pasteurization and Other Methods

- Holder Pasteurization: 62.5°C for 30 min, followed by rapid cooling to 4°C
- Vat Pasteurization: 62.8 ° for 30 min, followed by rapid cooling to 4°C
- High Temperature Short Time (HTST): 72°C for 16 sec
- Flash Heat
- High pressure processing (HPP)
- Thermo-ultrasonic processing
- UV-C irradiation
- Lyophilization

Frontiers in Pediatrics 2019. EMBA

Factors Influencing the Nutrient and Immuno-modulating Content of the Donor Milk

Pre-processing: stage of lactation, technique of expression, storage containers, duration of storage, shipping, thawing and pooling

Processing: Holder Pasteurization (62.5°C for 30 min, rapid cooling to 4°C). Milk Bank practices.

Post-processing: storage containers, duration of freezing, thawing, route of administration, fortification

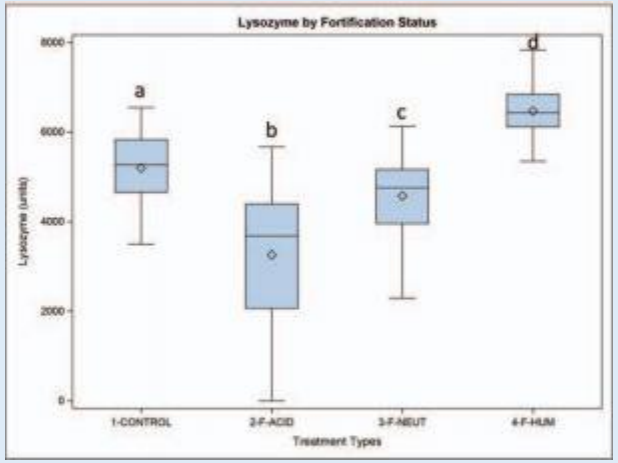
Effects of the Pasteurization Process on Breast Milk Components

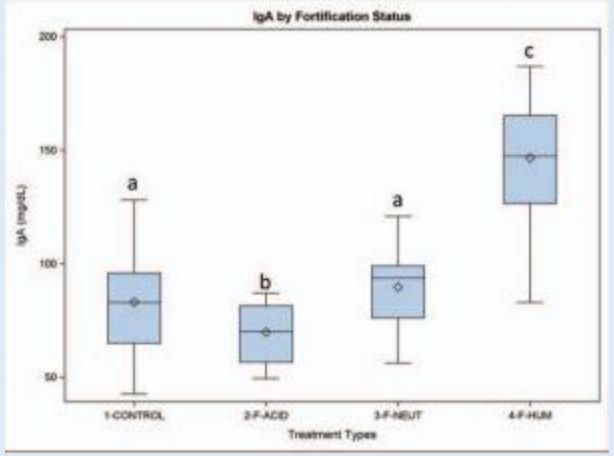
Component	Maintained >90%	Maintained 50-90%	Maintained 10-50%	Abolished
Macronutrients	Lactose Oligosaccharides	Protein Fat		
Micronutrients	Ca, Cu, Mg, Phos, K, Na, Zn	Fe		
Vitamins	Vit. A, Vit. D	Folate, Vit. B6, Vit. C		
Biologically active (immune)	IL-8, IL-12p70,IL-13, TGF-α	IgA, IgG, IGF-1, IGF-2, IGF-BP2,2, IFNɣ, IL-1beta, IL-4, IL-5, IL-10, TGF beta, Gangliosides	CD14 (soluble), IL-2, Lactoferrin, Lasozyme	Stem cells IgM, Lymphocytes Bacteria Viruses
Biologically active (metabolism)	Epidermal Growth Factor, Heparin Binding Growth Factor	Adiponectin, Amylase, Insulin	Erythropoietin, Hepatocyte Growth Factor	Bile Salt Dependent Lipase, Lipoprotein Lipase

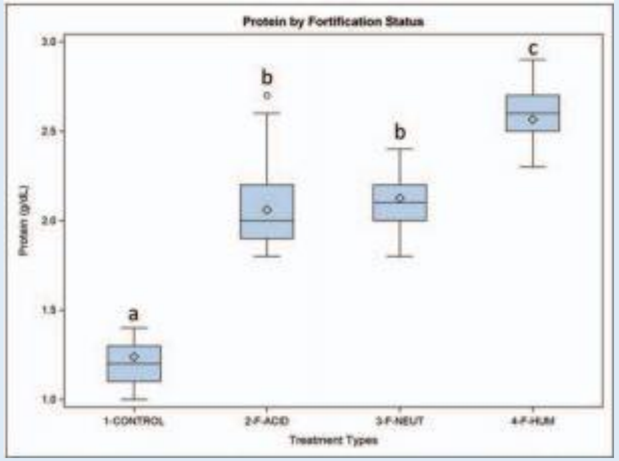
Human Milk Pasteurization: benefits and risks. O'Connor at al. Curr Opin Nutr Metab Care 2015

Effects of extended refrigeration and type of fortifier on the bacterial count and immunologic properties of donor milk

- Refrigeration at 4°C for 4 days does not increase bacterial count of defrosted unfortified and fortified DM. Donor milk refrigeration time extended to 48 hours
- Fortifiers:
  - Acidic fortifiers significantly lower the lysozyme and immunoglobulin A.
  - Human milk–derived fortifiers significantly increase the lysozyme and immunoglobulin A.
  - Refrigerated storage for up to 96 hours had no impact on the total protein, lysozyme activity, and immunoglobulin A.







Bacterial Content of Fortified and Unfortified Holder Pasteurized Donor Human Milk During Prolonged Refrigerated Storage. Cosmina Mandru, Maryanne T. Perrin, Radha Iyer, Dionysios Liveris, Ira Schwartz, Gad Alpan, Boriana Parvez. JPGN 2019;69: 487–492
The Effects of Fortification and Refrigerated Storage on Bioactive Proteins in Holder-Pasteurized Donor Human Milk. Hannah R. Schlotterer, Boriana Parvez MD, Maryanne T. Perrin PhD JPGN 2019;69: 370–374

Weight gain, lean body mass and protein gain during fetal life

Table. Nutritional needs by GA (weeks)

Variables (per kg/d)	GA, weeks <28	28-31	32-33	34-36	37-38	39-41
Fetal growth						
Weight gain, g	20	17.5	15	13	11	10
Lean body mass gain, g	17.8	14.4	12.1	10.5	7.2	6.6
Protein gain, g	2.1	2	1.9	1.6	1.3	1.2
Requirements						
Energy, kcal	125	125	130	127	115	110
Proteins, g	4	3.9	3.5	3.1	2.5	2
Calcium, mg	120-140	120-140	120-140	120-140	70-120	70-120
Phosphorus, mg	60-90	60-90	60-90	60-90	35-75	35-75

Weight gain, lean body mass, and protein gain during the last trimester of pregnancy and theoretical energy and protein requirements for enteral nutrition are indicated by GA group. Before 39 weeks' GA, requirements are based on fetal growth, fetal accretion rate, and intestinal absorption; after 40 weeks' GA, requirements are based on the composition of HM (adapted from Rigo[20] and Ziegler [21]). The values indicated in this table are theoretical values per GA groups. They show that both the late-preterm infant (ie, 34-36 weeks' GA) and the early-term infant (ie, 37-38 weeks' GA) have nutritional requirements that are different than the full-term infant (ie, 39-41 weeks' GA). The values indicated do not take into account the nutrient supply needed to compensate for any nutritional deficit and therefore are not applicable as such for the very preterm infant at time of, or after, hospital discharge.

Alexandre Lapillonne, Deborah L. O'Connor, Danhua Wang, Jacques Rigo, Nutritional Recommendations for the Late-Preterm Infant and the Preterm Infant after Hospital Discharge. The Journal of Pediatrics, Volume 162, Issue 3, Supplement, March 2013, Pages S90-S100, ISSN 0022-3476, http://doi.org/10.1016/j.jpeds.2012.11.058.

Nutritional recommendations in stable, fully enterally fed VLBW infants

Table 1. Current recommendations of advisable nutrient intakes for fully enterally fed preterm very low birth weight infants per kilogram per day, and per 100 kcal energy intake, compared to the previous intake recommendations of the US Life Science Research Office (for formula-fed preterm infants only) [2, 3], of Tsang et al., 2005 [4], and of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), 2010 [5]

Nutrient	Current recommendation (per kg/day)	Current recommendation (per 100 kcal)	LSRO, 2002 (formula-fed infants only, per kg/day)	Tsang et al., 2005 (per kg/day)	ESPGHAN, 2010 (per kg/day)
Fluids	135–200	–	NS	150–200	135–200
Energy, kcal	110–130 (85–95 i.v.)	–	100–141	110–120	110–135
Protein, g	3.5–4.5	3.2–4.1	3.0–4.3	3.0–3.6	4.0–4.5 (<1 kg) 3.5–4.0 (1–1.8 kg)
Lipids, g	4.8–6.6	4.4–6	5.3–6.8		4.8–6.6 (<40% MCT)
Carbohydrate, g	11.6–13.2	10.5–12	11.5–15.0 lactose 4.8–15.0	lactose: 3.8–11.8 oligomers: 0–8.4	11.6–13.2
Calcium, mg	120–200	109–182	148–222	120–230	120–140
Phosphate, mg	60–140	55–127	98–131	60–140	60–90

Tsang R, Uauy R, Koletzko B, Zlotkin S (eds): Nutrition of the Preterm Infant. Scientific Basis and Practical Application, ed 2. Cincinnati, Digital Educ Publ, 2010, pp 97–139.

Recommended macro/micronutrient requirements

Table 1
Recommended macronutrient/micronutrient requirements (units/kg/d) for the stable preterm infant

	Term	ELBW	VLBW	VLBW Postterm
Energy, kcal	90–120	130–150	110–130	90–100
Protein, g	1.52	3.8–4.4	3.4–4.2	2.0
Carbohydrate, g	16–20[a]	9–20	7–17	6.8–14.1
Fat, g	8–10.3[a]	6.2–8.4	5.3–7.2	4.0–6.6
Vitamin A, IU	1333	700–1500	700–1500	545–1273
Vitamin D, IU	200	150–400	150–400	400
Calcium, mg	70–120	100–220	100–220	253–377
Phosphorus, mg	35–75	60–140	60–140	105–273
Iron, mg	0.09[a]	2–4	2–4	1.8–2.7
Zinc, μg	666[a]	1000–3000	1000–3000	890

[a] For an average term infant 0–6 months of age.
Data from Refs.[2,18,24,29,38–40]

Nzegwu, Ehrenkranz, Post Discharge Nutrition and the VLBW infant: To supplement or not to supplement? Clinical Perinatology 41. 2014

The final macronutrient and caloric content depends on the composition of the base milk and the fortifier

Term EBM (Ballard)	Protein g/100 ml	CHO g/100 ml	Fat g/100 ml	kCal/100 ml
Term EBM	0.9	6.7	3.5	59
Prolact+4	1.92	7.16	4.6	75
Prolact+6	2.43	7.49	5.15	83
Prolact+8	2.94	7.62	5.70	91
HMF (MJ/Enfamil) 22	1.82	6.64	4.23	70
HPCL (Abbott/Similac) 22	1.73	7.45	3.56	66
HMF (MJ/Enfamil) 24	2.58	6.58	4,83	78
HPCL (Abbott/Similac) 24	2.50	8.08	3.62	72

Preterm EBM (Hartman)	Protein g/100 ml	CHO g/100 ml	Fat g/100ml	kCal/100ml
Preterm EBM	1.4	6.7	4.2	68
Prolact+4	2.32	7.16	5.16	82
Prolact+6	2.78	7.49	5.64	89
Prolact+8	3.24	7.62	6.12	96
HMF (MJ/Enfamil) 22	2.27	6.64	4.86	77
HPCL (Abbott/Similac) 22	2.18	7.45	4.2	74
HMF (MJ/Enfamil) 24	3.0	6.58	4.58	77
HPCL (Abbott/Similac 24	2.83	8.08	4.2	79

Intakes of key nutrients from various enteral nutrition feedings for preterm infants in the United States, assuming milk intake of 160 mL/kg per day

	Target intake*	Unfortified human milk ¶Δ (≈20 kcal/oz)	Human milk with liquid bovine-derived HMF ¶◊ (≈24 kcal/oz)	Human milk with donor human milk-derived HMF § (≈26 kcal/oz)	Preterm formula (24 kcal/oz)
Energy (kcal/kg/day)	128	104	128	138	129
Protein (g/kg/day)	3.5 to 4	1.6	4.1 to 4.3	3.8	4.3 to 4.6
Fat (g/kg/day)	5 to 7	5.6	6.3 to 8.3	8.3	5.6 to 7.0
Carbohydrate (g/kg/day)	12 to 14	11.2	11.2 to 13.6	13.4	12.9 to 13.6
Calcium (mg/kg)	150 to 220	40	192 to 197	195	210 to 234
Phosphorus (mg/kg)	75 to 140	22	103 to 110	102	117 to 129
Vitamin D (international units/day)	400	0.3	189 to 253	64	194 to 384

* Recommendations for preterm infants weighing 1000 to 1500 g.
¶ Human milk data are based on mature human milk.
Δ For human milk, the energy content is based on mean content of 65 kcal/dL; protein content is based on mean of 1 g/dL; fat content is based on mean of 3.5 g/dL; and carbohydrate content is based on a mean of 11.5 to 13 g/dL.[2]
◊ Nutrition information for bovine-derived human milk fortifier (HMF) is based upon common liquid HMF available in the United States.[2]
§ Nutrition information for human donor-derived HMF is based upon Prolacta+6 brand (Prolacta Bioscience).[4]

References:

1. *Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr 2014; 14:216.*
2. *American Academy of Pediatrics. Pediatric Nutrition Handbook, 7th ed, Kleinman RE, Greer FR (Eds), American Academy of Pediatrics, Elk Grove Village 2014.*
3. *Koletzo B, Poindexter B, Uauy R. Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. World Review of Nutrition and Dietetics Vol. 110. Switzerland. 2014.*
4. *Guidelines for Acute Care of the Neonate, 26th edition (2018-2019), Fernandes CJ, Pammi M, Katakam L , et al (Eds), Baylor College of Medicine, Houston, 2014*

B. Parvez.

Growth in NICU

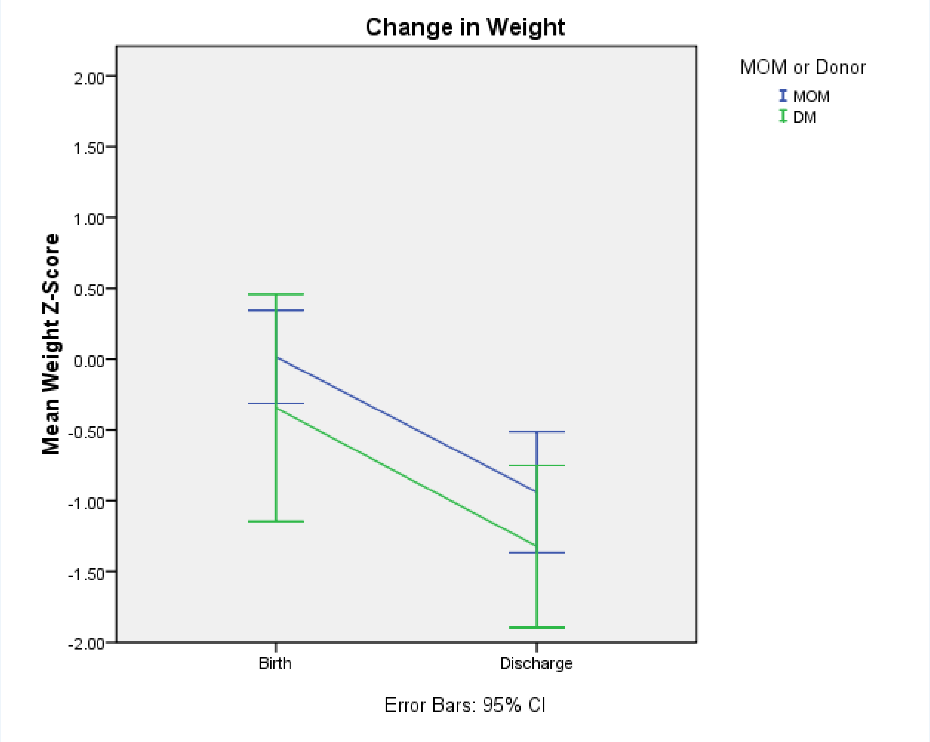
- Genetically predetermined but can be affected by various environmental factors: maternal, intrauterine, postnatal
- Increase in weight, length and head size over time
- Velocity is tracked based on GA and CGA, Fenton 2013 Growth Chart
- Formula fed neonates have faster growth velocity
- Older studies show that slow growth velocity in NICU has been associated with neurodevelopmental delay (Lemon J, Alexander L, Cook D, Ehrenkranz R)
- IUGR, SGA without catch up growth is associated with developmental delays(Levine T, Hack M)
- Growth can be improved by specific nutritional interventions (Hair A) or by “bundle” QI approach (Stevens T)
- The neurodevelopmental outcome of ELBW fed exclusive human milk diet is not affected by EUGR status. (Rahman A)

1. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Pediatrics 2006;118:1078-86.
2. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Pediatrics 2006;117:1253-61
3. Neurodevelopmental Outcome of Extremely Low Birth Weight Infants Fed an Exclusive Human Milk Diet Is Not Affected by Growth Velocity. Amanda Rahman, Jordan S Kase , Yuanyi L Murray , Boriana Parvez. Breastfeeding Medicine. 2020 Jun;15(6).
4. Formula versus donor breast milk for feeding preterm or low birth weight infants. Quigley M, Embleton ND, McGuire W.Quigley M, et al. Cochrane Database Syst Rev. 2018 Jun 20;6(6):CD002971

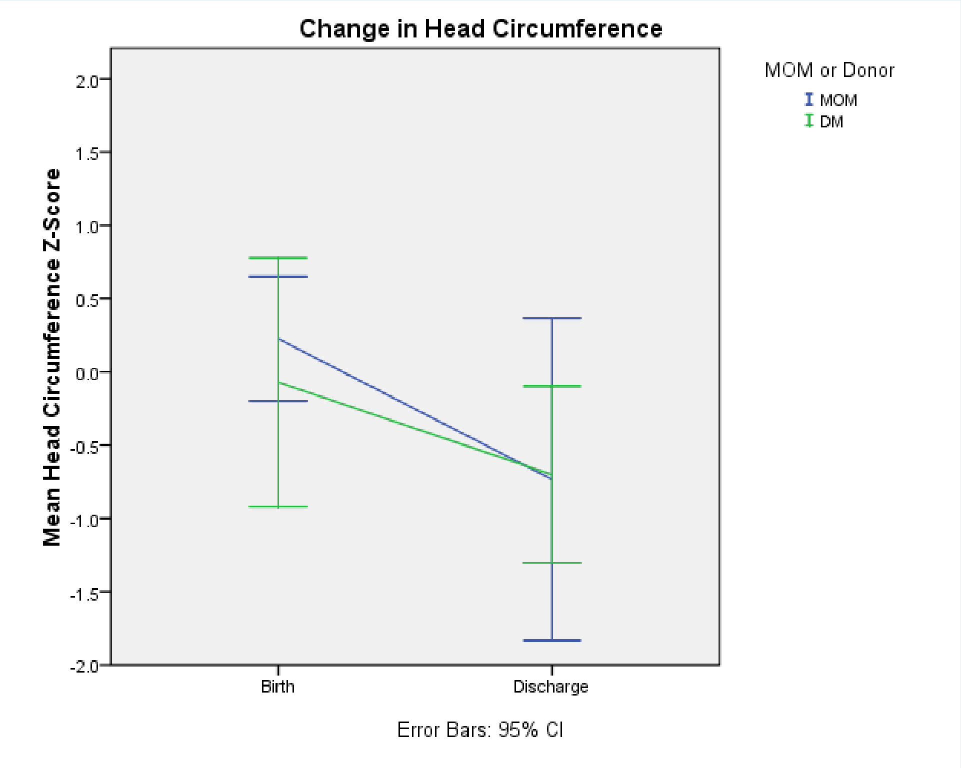
Donor milk diet is associated with slow growth

- Dose-response Relationship Between Donor Human Milk, Mother's Own Milk, Preterm Formula, and Neonatal Growth Outcomes
  - 314 VLBW infants were studied. Using MOM as reference, for every 10% increase in DHM intake, the adjusted mean growth velocity for weight significantly decreased by 0.17 g/kg/day
  - The adjusted mean change in weight z score significantly decreased with increasing proportion of DHM intake but significantly improved with increasing PF intake
  - The adjusted mean head circumference velocity was significantly decreased by 0.01 cm/wk for every 10% increase in DHM intake, in reference to MOM, but did not vary with PF intake. Neither proportion of DHM nor PF intake was associated with length velocity
- Growth Benefits of Own Mother's Milk in Preterm Infants Fed Daily Individualized Fortified Human Milk
  - HM types (raw OMM, pasteurized OMM, and DM) influence on growth was evaluated in 101 preterm infants (birth weight 970 ± 255 g, gestational age 27.8 ± 1.9 weeks)
  - Energy (143 ± 8 vs. 141 ± 6 kcal/kg/day) and protein intakes (4.17 ± 0.15 vs. 4.15 ± 0.14 g/kg/day were similar in both groups
  - Infants receiving predominantly OMM (n = 37), gained more weight (19.8 ± 2.0 vs. 18.2 ± 2.2 g/kg/day; p = 0.002) and length (1.17 ± 0.26 vs. 0.99 ± 0.36 cm/week; p = 0.020) than those fed predominantly DM (n = 33)
  - Stepwise multivariate analysis (n = 101) suggests that raw OMM was the major determinant of growth, contributing 22.7% of weight gain. Length gain was also related to OMM (raw + pasteurized) intakes, explaining 4.0% of length gain

Brownell EA. J Pediatr Gastroenerol Nutr 2018
De Haleux V. Nutrients 2019



29 MOM
12 DM



Weight			
MOM	Initial Z-score 0.02	DC Z-score -0.94	p<0.001
	Change in Z-score: -0.96		
DM	Initial Z-score -0.34	DC Z-score -1.32	p<0.001
	Change in Z-score: -0.98		
Maternal vs. Donor Milk Z-score			p = 0.936

Head Circumference			
MOM	Initial Z-score 0.23	DC Z-score -0.73	p = 0.020
	Change in Z-score: -.96		
DM	Initial Z-score -0.07	DC Z-score -0.70	p = 0.137
	Change in Z-score: -0.63		
Maternal vs. Donor Milk Z-score			p = 0.483

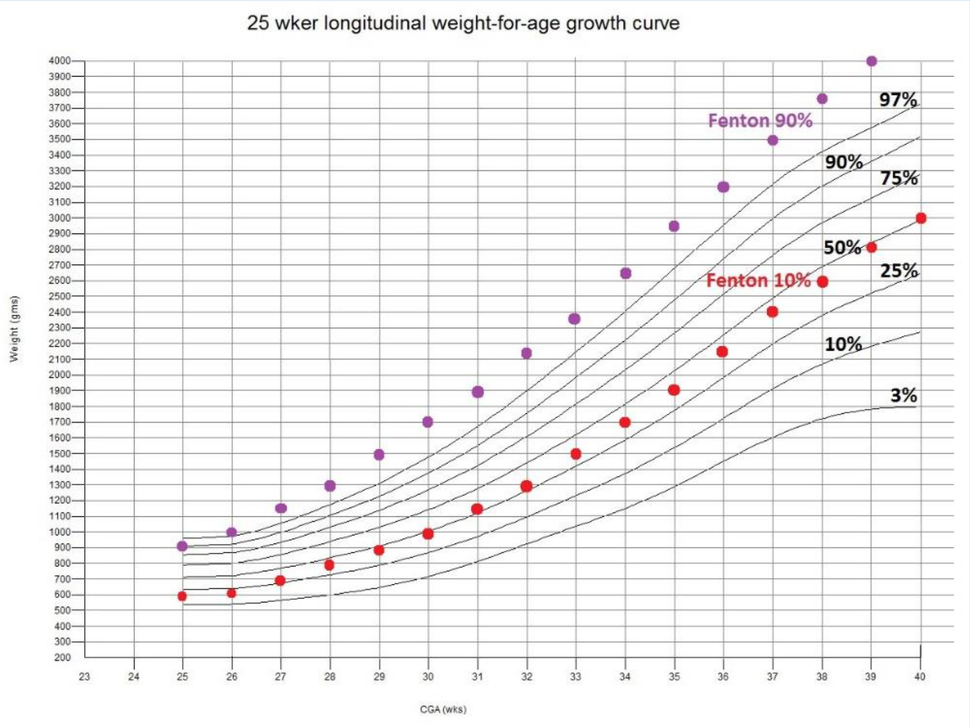
A. Rahman, B. Parvez et al. PAS 2017

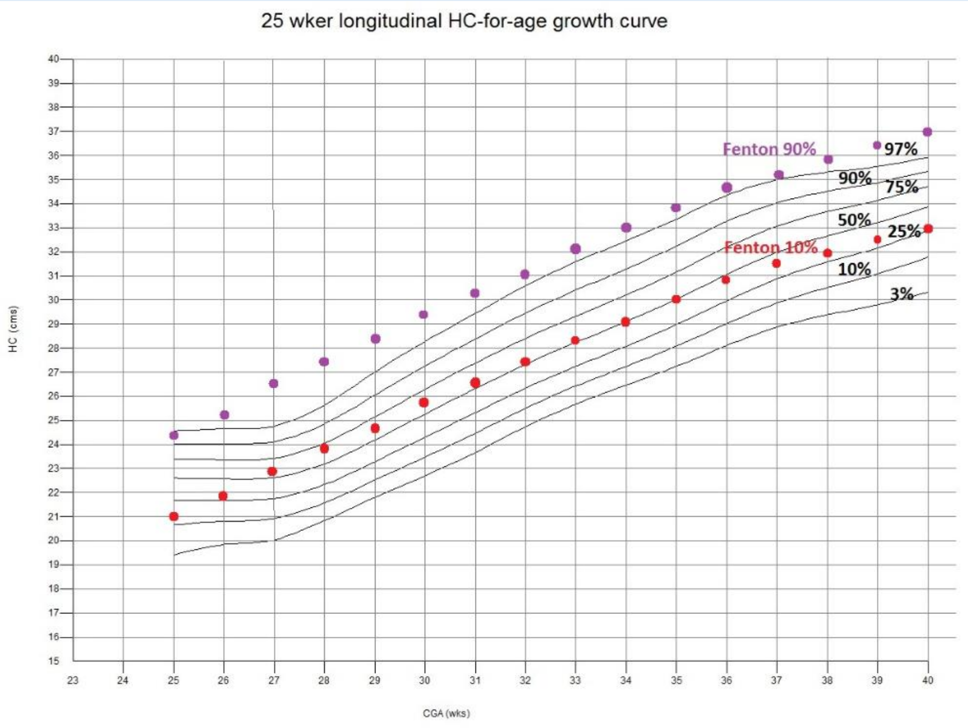
Currently Available Growth Charts

Assumption: Extrauterine growth should mimic that in the uterus

Term	Preterm	EHM
Euro-Growth Study, 2000	**Fenton, 2013**	Intergrowth-21st, 2015
CDC, 2000	Intergrowth-21st, 2015	Aprile et al, 2010
WHO, 2005	Ehrenkranz, 1996	
	Vanderbilt, 1997	
	Oslen, 2010	

EUGR Rate						
GA, weeks	23 (n=14)	24 (n=24)	25 (n=35)	26 (n=28)	27 (n=13)	28 (n=17)
EUGR at 40 wks Fenton 2013	9 (64%)	11 (46%)	7 (20%)	10 (36%)	5 (38%)	127 (71%)
EUGR at 40 wks The New Curve	1 (7%)	2 (8%)	3 (9%)	2 (7%)	2 (15%)	1 (6%)





Murray L, Rahman A, Alpan G, Parvez B

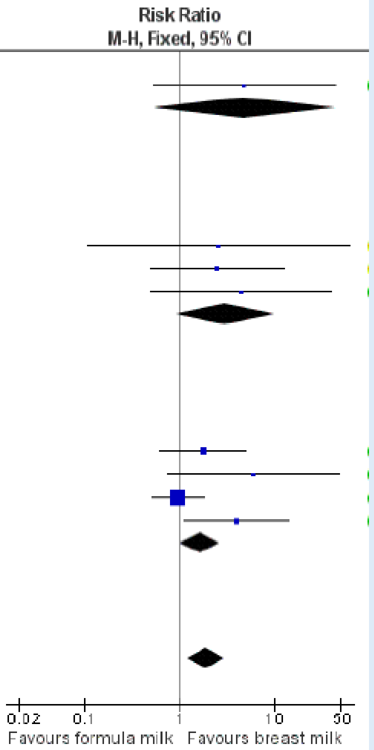
Preterm or term formula feeding in preterm infants is associated with faster growth but higher incidence on NEC

- 11 trials, 1809 infants, 1976-2017
- Comparing term or preterm formula feeding with fortified or unfortified donor milk (only one study of unpasteurized DM)
- Only 4 trials of nutrient enriched DM
- MD in weight gain 2.51 g/kg/day (95% CI 1.93 to 3.08)
- MD in linear growth 1.21 mm/week (95% CI 0.77 to 1.65)
- MD in head growth 0.85 mm/week (95% CI 0.47 to 1.23)
- No effect on long-term growth or neurodevelopment
- Formula feeding increased the risk of necrotizing enterocolitis (typical risk ratio (RR) 1.87, 95% CI 1.23 to 2.85; risk difference (RD) 0.03, 95% CI 0.01 to 0.06)

Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD002971.

Elimination of bovine protein reduces NEC

Study or Subgroup	Formula milk Events	Formula milk Total	Donor breast milk Events	Donor breast milk Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.25.1 Term formula versus unfortified DBM							
Gross 1983	3	26	1	41	2.5%	4.73 [0.52, 43.09]	1983
Subtotal (95% CI)		**26**		**41**	**2.5%**	**4.73 [0.52, 43.09]**	
Total events	3		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.38 (P = 0.17)							
1.25.2 Preterm formula versus unfortified DBM							
Tyson 1983	1	44	0	37	1.8%	2.53 [0.11, 60.39]	1983
Lucas 1984b	5	173	2	170	6.5%	2.46 [0.48, 12.49]	1984
Lucas 1984a	4	76	1	83	3.1%	4.37 [0.50, 38.23]	1984
Subtotal (95% CI)		**293**		**290**	**11.4%**	**2.99 [0.90, 9.87]**	
Total events	10		3				
Heterogeneity: Chi² = 0.18, df = 2 (P = 0.91); I² = 0%							
Test for overall effect: Z = 1.80 (P = 0.07)							
1.25.3 Preterm formula versus fortified DBM							
Schanler 2005	10	88	5	78	17.2%	1.77 [0.63, 4.96]	2005
Cristofalo 2013	5	24	1	29	2.9%	6.04 [0.76, 48.25]	2013
Corpeleijn 2016	17	190	17	183	56.2%	0.96 [0.51, 1.83]	2016
O'Connor 2016	12	182	3	181	9.8%	3.98 [1.14, 13.86]	2016
Subtotal (95% CI)		**484**		**471**	**86.1%**	**1.64 [1.03, 2.61]**	
Total events	44		26				
Heterogeneity: Chi² = 6.12, df = 3 (P = 0.11); I² = 51%							
Test for overall effect: Z = 2.09 (P = 0.04)							
Total (95% CI)		**803**		**802**	**100.0%**	**1.87 [1.23, 2.85]**	
Total events	57		30				
Heterogeneity: Chi² = 8.17, df = 7 (P = 0.32); I² = 14%							
Test for overall effect: Z = 2.92 (P = 0.004)							
Test for subgroup differences: Chi² = 1.57, df = 2 (P = 0.46), I² = 0%							



Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD002971

Sullivan S: 207 infants, 2 groups MM/donor milk fortified either with human milk derived fortifier (HUM) at 40 ml/kg and 100 ml/kg vs. MM with BOV fortifier and preterm formula

- Significant reduction in NEC (50%) and surgical NEC (90%)

An exclusive human milk diet is associated with lower rate of NEC than diet with human milk and bovine milk based products. Sullivan S et al. J Pediatr 2010

Costs of NEC and cost-effectiveness of exclusive human milk diet in ELBW Infants

- Cost of NEC
  - $74,004 for medical NEC, $198,040 for surgical NEC [1]
  - Direct savings $8,167.17 per infant [1]
  - $276,076 (peritoneal drain), $398,173 (peritoneal drain followed by laparotomy), $341,911 (laparotomy) [2]
- For every $1 spent on donor milk, $11 are saved [3]:
  - Reduced hospital stay, reduced sepsis and NEC
  - Reduced feeding intolerance and TPN
  - Reduced long term morbidities
- An EHM diet is clinically beneficial and generates substantial cost savings: $16,309/infant from reduction of morbidities and up to $117,239/per infant when wider societal costs are included[4]

[1] Ganapathy V. Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. Breastfeed Med. 2012 Feb;7(1):29-37
[2] Stey A. Outcomes and Costs of Surgical Treatment of NEC. Pediatrics. 2015 May; 135 (7): 1191-1197
[3] Arnold LD. The cost-effectiveness of using banked donor milk in the neonatal intensive care unit: prevention of necrotizing enterocolitis. J Hum Lact. 2002 May;18(2):172-7
[4] An economic analysis of human milk supplementation for very low birth weight babies in the USA Grace Hampson. BMC Pediatrics 2019

Exclusive Human Milk Diet and Feeding Tolerance

- Single center observational study, 293 infants, GA 23 - 34 weeks, BW 490 - 1700 g
  - 30% received EHM diet with mother's or donor milk and donor milk-derived fortifier
  - 43% received mother's milk with bovine based milk fortifier,
  - 17% had formula/ mother's milk with bovine-based milk fortifier
  - 10% were fed an exclusive formula diet
- Results:
  - 94% of EHM diet never had feedings held
  - 10 days longer to achieve full feeds in all mixed diets
  - 22 days longer hospitalization in all mixed diets
  - 10 fold decrease in NEC with EHM diet
  - $106,968 per infant lower hospital costs

Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. Assad M. Journal of Perinatology (2016) 36, 216–220

Human milk feeding is associated with higher lean body mass as compared to formula

Study	Type of Study	Population	Timing of Evaluation	Principal Aim	Method of Assessment	Main Findings
Giannì et al. [14]	Observational cohort study	n = 284, GA 34–36 weeks	At term CGA	Body composition in late preterms infants fed with exclusively MM/any MM vs. FM	Air-displacement pletysmograph (PEA POD Infant Body Composition System)	Positive association of any MM feeding at discharge and at term CGA and exclusively MM feeding at term CGA with FFM content (β =−47.9, 95%, CI = −95.7; −0.18; p = 0.049; β = −89.6, 95% CI = −131.5; −47.7; p < 0.0001; β= −104.1, 95% CI = −151.4; −56.7, p < 0.0001)
Piemontese et al. [15]	Longitudinal observational study	n = 73, VLBW< 1500 g, GA 26–34 weeks	At term CGA	Body composition in VLBW preterm infants fed with HM at < 50% vs. HM ≥ 50% of the total volume intake	PEA POD Infant Body Composition System	Positive association between the HM % and FFM % after correction for birth weight and gender (β = 0.12 ± 0.05, p = 0.01) Increase in FFM % at term GCA when HM ≥ 50% (p = 0.01)
Morlacchi et al. [16]	Prospective observational study	n = 32, VLBW< 1500 g, GA ≤ 32 weeks	At discharge and at term CGA	Body composition and protein balance in VLBW premature neonates exclusively MM vs. FM fed	PEA POD Infant Body Composition System Standard nitrogen balance method; Infrared spectroscopy analysis to assess nutritional composition of the MM; for FM, macronutrients calculated based on manufactures' info	At discharge, higher nitrogen balance in MM-fed infants compared with FM fed (mean 488.3 ± 75 compared with 409.8 ± 85 mg kg^{-1} d^{-1}, p = 0.009) At term CGA, in MM-fed compared to FM-fed infants higher FFM % (85.1 ± 2.8 vs. 80.8 ± 3.2, p = 0.002), lower ATM % (14.9 ± 2.8 vs. 19.2 ± 3.2, p = 0.002), lower ATM (458 ± 118, p = 0.004) FFM independently associated with MM feeding (R^2 = 0.93, p < 0.0001)
Mól et al. [17]	Prospective cohort study	n = 53, VLBW 1000–1500 g	At birth and at term CGA	Body composition of VLBW newborns fed with either MM or FM compared to full-term infants	Multi-frequency impedance body composition monitor	In the FM-fed VLBW preterms compared to full-term newborns lower FFM % (83.5 vs. 85.5, p < 0.001), higher ATM % (16.4 vs.14.5, p < 0.01) and higher ATM kg (0.617 ± 0.18 vs. 0.494 ± 0.1, p = 0.02) No differences in FFM or FM between the HM fed VLBW infants and the term newborns

Human milk (HM) = own mother's or maternal milk (MM) and donor milk (DM) fed; Formula milk = FM; Gestational age (GA); Corrected gestational age (CGA); Very low birth weight infants (VLBW); Adipose tissue mass (ATM); Fat-free mass (FFM); CI (Confidence Interval).

Carlacchi J. Nutrients 2020

Exclusive Human Milk Diet with MOM, DM and HUM fortifier improves development in ELBW

- Exclusive human milk diet is protective in the settings of EUGR. [1]
  - Prospective cohort of ELBW fed exclusive human milk diet with MOM, DM, HUM fortifier, assessed with BSID-III at 19 months of age
  - Neurodevelopmental outcome between the EUGR and non EUGR infants was similar in all domains (gross and fine motor, language and cognitive)
- There is a significant dose-dependent association between NICU HM intake and cognitive scores at 20 months CA [2]
  - Cohort study of ELBW infants
  - After multivariable linear regression analyses controlled for neonatal and social risk factors, the authors found that each 10 mL/kg/day increase in NICU HM-DD was associated with a 0.35 increase in cognitive index score (95% CI [0.03-0.66], p = 0.03)
- EHM diet supports similar growth and neurodevelopmental outcome in ELBW infants. [3]
  - BOV and EHM groups cohorts. BW 700 g, GA 27 weeks
  - Growth until discharge: 12 vs 13 g/kg/day and similar growths post discharge
  - BSID-III scores: 97±16 vs 98±14

1. Neurodevelopmental Outcome of Extremely Low Birth Weight Infants Fed an Exclusive Human Milk Diet Is Not Affected by Growth Velocity. Amanda Rahman, Jordan S Kase , Yuanyi L Murray , Boriana Parvez. Breastfeeding Medicine. 2020 Jun;15(6):362-369.
2. NICU Human Milk Dose and 20-Month Neurodevelopmental Outcome in Very Low Birth Weight Infants. Patra Kousiki, Aloka Patel. Neonatology 2017, 112(4):330-336
3. Growth and development in ELBW infants after the introduction of EHM feedings. Michael Colacci. Am J Perinatol. 2017

Reassuring data: Not only leaner but with better brains

- 898 preterm <30 week VLBW infants
  - Bayley-III Cognitive Composite score < 80 at 21-months CGA and Wechsler Preschool and Primary Scale of Intelligence Quotient <70 at 36-months CGA, were determined using receiver operating characteristic (ROC) curves
  - At 36 weeks CGA weight, length or head circumference <10th or <3rd % did not predict cognitive impairment; areas under ROC curves were <0.6. Sensitivities and specificities for 10th and 3rd percentile cut points were all poor, with most not exceeding 70%, whether the Fenton 2013 or INTERGROWTH 2015 growth charts were used
  - Brain injury and low maternal education were better predictors of cognitive impairment
- 47 preterm infants with CGA 29 weeks (23-33)
  - 27 infants received ≥75%, 20 infants < 75% of human milk of days of in-patient care
  - Higher connectivity in the fractional anisotropy (FA)-weighted connectome in the exclusively human milk fed infants
- 68 infants, BW <1500 g, GA <32 weeks: 44 human milk (MOM and PDHM) and 24 formula fed in the first weeks of life
  - Significantly larger total brain volumes , volumes in the amygdala-hippocampus and cerebellum and greater white matter microstructural organization in the corpus callosum, posterior limb of internal capsule and cerebellum

Weight, length, and head circumference at 36 weeks are not predictive of later cognitive impairment in very preterm infants. Fenton, T.R., Nasser, R., Creighton, D. *et al. J Perinatol* (2020).
Early breast milk exposure modifies brain connectivity in preterm infants. Blessa M, Sullivan G, Anblagan D, Telford EJ, Quigley AJ, Sparrow SA et all. Neuroimmage. 2019; 184:431-9
Improved brain growth and microstructural development in breast milk fed very low eight premature infants. Ottolini KM, Andescavage N, Kapse K, Jacobs M, Limperopoulos C. Acta Paediatr. 2020; 109:1580-87

EHM diet protects against severe IVH

Neonatal Morbidities and Outcomes			
	EHM (N=126)	BOV (N=180)	p
Survival to DC, n (%)	113 (90)	153 (85)	NS
CA at DC in weeks, mean (SD)	39 (±6)	39 (±7)	NS
LOS in days of survivors, mean SD)*	105 (±30)	104 (±46)	NS
NEC, n (%)	6 (5)	31 (17)	0.001
Severe ROP, n (%)	10 (8)	9 (5)	NS
PDA ligation, n (%)	21 (17)	27 (15)	NS
Oxygen at DC, n (%)	48 (38)	68 (38)	NS
Sepsis, n (%)	17 (13)	31 (17)	NS
*EHM n=113, BOV=153			

Incidence of IVH/PVL			
	EHM (N=127)	BOV (N=179)	p
Severe IVH and/or PVL, n (%)	9 (7)	32 (18)	0.004
Severe IVH only, n (%)	4 (3)	16 (9)	0.147
PVL only, n (%)	2 (1.6)	1 (0.6)	
Severe IVH and PVL, n (%)	3 (2)	15 (8)	
DOL of IVH, median (IQR)	2 (1-8)	2 (2-5)	NS

Severe IVH/PVL without NEC	**EHM (N=121)**	**BOV (N=148)**	**p**
Severe IVH and/or PVL, n (%)*	6 (5)	22 (14.9)	0.009
Severe IVH only, n (%)	4 (3.3)	10 (6.8)	0.273
PVL only, n (%)	0	0	NA
Severe IVH and PVL, n (%)	2 (1.6)	12 (8.1)	0.025

After adjusting for antenatal steroids and NEC the BOV group had 2.7 times higher odds of brain injury when compared to the EHM group (95% CI 1.2-6.0)

Exclusive human milk diet reduces incidence of severe intraventricular hemorrhage in extremely low birth weight infants. Carome K, Rahman A, Parvez B. J Perinatol. 2020

Exclusive Human Milk Diet with MOM, DM and HUM fortifier

- RCT of 232 VLBW infants: 127 in HUM, 63 in BOV fortifier, diet with MOM and DM (CIHR funded, DoMINO trial)
  - No differences in feeding intolerance, morbidities, growth and stool calprotectin
  - 80% of the diet with MOM in both groups
- Neurodevelopmental outcome follow up and EHM diet (OPTIMOM study)
  - 64 HUM and 63 BOV
  - BSID-III: 94.7 in HUM vs 93.1 in BOV
  - 87% of diet with MOM

O'Connor D. Am J Clin Nutr 2018
Hopparton KE. Curr Dev Nutr 2019

Donor Milk Protects against BPD

- Eighteen studies were evaluated met the inclusion criteria
- Observational studies (8 studies – Spiegler, Kreissl, Sisk, Lee, Ginovart, Assad, Colacci, Hair): DM supplementation reduced BPD, RR 0.78 (95% CI 0.67–0.90)
- EHM diet reduced BPD when compared to a diet with PF and/or bovine milk-based fortifier (three studies – Cristofalo, Sullivan, Schanler): RR 0.80 (95% CI 0.68–0.95)
- Raw MOM diet compared to feeding pasteurized MOM (2 studies – Cossey, Dicky) protected against BPD (two studies): RR 0.77 (95% CI 0.62–0.96)
- RCTs (three studies - Schanler, Sullivan, O'Connor)): MOM supplemented with DM did not reduce BPD when compared to PF, RR 0.89 (95% CI 0.60–1.32)

Donor Human Milk Protects against Bronchopulmonary Dysplasia: A Systematic Review and Meta-Analysis. Eduardo Villamor-Martínez. Nutrients 2018

Donor Milk and ROP

Medline, PubMed, and EBSCO search for articles published through February 2015
Five studies with 2208 preterm infants OR with 95% CI were:

Any-stage ROP:

- **exclusive human milk** versus any formula, 0.29 (0.12 to 0.72)
- **exclusive human milk** versus exclusive formula, 0.25 (0.13 to 0.49)
- mainly human milk versus mainly formula, 0.51 (0.26 to 1.03)
- any human milk versus exclusive formula, 0.54 (0.15 to 1.96)

Severe ROP:

- **exclusive human milk** versus any formula: 0.11 (0.04 to 0.30)
- **exclusive human milk** versus exclusive formula : 0.10 (0.04 to 0.29)
- **mainly human milk** versus mainly formula: 0.16 (0.06 to 0.43)
- any human milk versus exclusive formula : 0.42 (0.08 to 2.18)

Based on current limited evidence, in very preterm newborns, human milk feeding **potentially plays a protective role in preventing any-stage ROP and severe ROP**.

Human Milk Feeding as a Protective Factor for Retinopathy of Prematurity: A Meta-analysis. Zhou J. PEDIATRICS Volume 136, number 6, December 2015

maria Fareri children's Hospital
AT WESTCHESTER MEDICAL CENTER

Westchester
MEDICAL CENTER

Liquid Gold Preemie Milk Bank
“Support the Mothers; Nourish the Babies”

Our Philosophy: Mother’s milk is the ideal nutrition for all babies and especially preemies. Preterm human donor milk is the supplement of choice when mother’s own milk is unavailable or insufficient and serves as a “bridge” until lactation is established.

Our Mission:
- Support all mothers’ ability to nourish, nurture and care for their babies
- Provide safe preterm pasteurized donor human milk for high risk neonates in need
- Educate parents, families, communities and healthcare providers about the benefits of breastfeeding, mothers’ milk and donor milk
- Advance knowledge through research

Our Milk Bank Staff:
Tina Roeder RN, MSN, CNS, IBCLC
Artie Hariprasad
Boriana Parvez MD. IBCLC

Advisory Board:
Edmund F. LaGamma MD
Heather Brumberg MD
Sheila Nolan MD


WMC Preterm Milk Bank is One year old (10/8/2019 – 10/8/2020)

1. Dispensed PDHM:
   a) **Preterm:** 189, 980 ml (6333 oz): Carbohydrate 7.2 ± 0.2 g/100 ml; Protein 1.2 ± 0.3 g/100 ml; Fat 3.9 ± 0.4 g/100 ml, Calories: 72 ± 4 kcal/100 ml (22 Cal/oz)
   b) **Term:** 128, 300 ml (4277 oz): Carbohydrate 7.3 ± 0.1 g/100 ml; Protein 0.9 ± 0.1 g/100 ml; Fat 3.3 ± 0.3 g/100 ml, Calories: 64 ± 3 kcal/100 ml (19 Cal/oz
2. Recipients: 90 infants
3. Billing: $54, 107 (Net profit from not ordering donor milk from outside milk bank and concurrent billing)
4. Approved donors: 18
5. Significant reduction of NEC and IVH

Summary

- Human milk feeding is associated with decreased morbidities (NEC, BPD, ROP, IVH) in preterm infants
- Human milk feeding is associated with improved lean body mass and increased brain connectivity and brain size, as well as IVH
- Neurodevelopmental outcome of preterm infants is improved when bovine protein is avoided and also in the settings of high intake of MOM
- Postnatal growth restriction in the “age of breast milk diet” doesn’t have negative effect on neurodevelopment
- Very limited data comparing exclusive MOM and DM diets
- No studies of preterm DM

THANK YOU!

Questions, Suggestions and Comments

Tamaya (BW 265 grams) celebration her first year birthday with us!

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Availability of Donor Milk Increases Breastfeeding Rates

- Arslanoglu S: Italian NICUs, 46-47% in the North, 26% in the south offer donor milk
  - Exclusive BF: 16 vs. 30%
  - Any BF: 53 vs. 60%
- Kantowska A: California, 2007 vs. 2013
  - 50% increase in number of hospitals using donor milk use
  - 81% of premature infants had access to donor milk
  - 10% exclusive breastfeeding rates
  - 2.6% decrease in NEC

Presence of human milk bank is associated with elevated rates of exclusive breastfeeding. Arslanoglu S. J. Perinat. Med 2013
Impact of Donor Milk Availability on Breast Milk Use and NEC. Kantowska A. Pediatrics 2016

Breast Milk: Liquid Gold

- Human milk diet has been shown to be associated with a decreased incidence of NEC, ROP, and sepsis[1-3].

- Breast milk, and colostrum, contain neuroprotective factors:
  - Vascular Endothelial Growth Factor[4]
  - Epidermal growth factor[5,6]
  - Transforming Growth Factor β[7]
  - Mesenchimal Stem Cells

- Even after pasteurization, donor milk maintains many of its biologically active factors, which may still provide neuroprotection[8]

1. Quigley MM. Cochrane Database Syst Reviews. 2014.
2. Hylander MA et al. Journal of Perinatology. 2001.
3. Ronnestad A et al. Pediatrics. 2005;115(3):e269-e276.
4. Patki S et al. Cytokine, 2012.
5. Dvorak B et al. Pediatric Research, 2003.
6. Liu B et al. Journal of Neuroscience Research, 2007.
7. Ballabh P. Pediatric Research, 2010.
8. Oconnor et al. Current Opinion in Clinical Nutrition and Metabolic Care, 2015

EHM diet protects against severe IVH

Maternal Characteristics		
	EHM (N=127)	BOV (N=179)
Age, years, mean (SD)	30 (±7)	30 (±6)
White race, n (%)	49 (39)	49 (27)
Antenatal steroids, n (%)	113 (89)	142 (79)*
Preeclampsia, n (%)	26 (20)	30 (17)
PPROM, n (%)	32 (25)	55 (31)
Chorioamnionitis, n (%)	21 (17)	23 (13)
C-section, n (%)	79 (62)	114 (64)

*$p < 0.05$

Neonatal Characteristics		
	EHM (N=127)	BOV (N=179)
Male, n (%)	64 (50)	81 (45)
Multiple gestation, n (%)	34 (27)	47 (26)
Inborn, n (%)	109 (86)	146 (82)
5 min APGAR <3, n (%)	14 (11)	18 (10)
GA in weeks, mean (SD)	26 (±2)	26 (±2)
BW in grams, median (IQR)	770 (630-880)	770 (660-880)
SGA, n (%)	14 (11)	22 (12)
HC in cm at birth, mean (SD)	22.6 (±1.8)	22.7 (±1.7)

BOV: any exposure to cow milk based protein from preterm formula or cow milk based fortifier

Exclusive human milk diet reduces incidence of severe intraventricular hemorrhage in extremely low birth weight infants. Carome K, Rahman A, Parvez B. J Perinatol. 2020

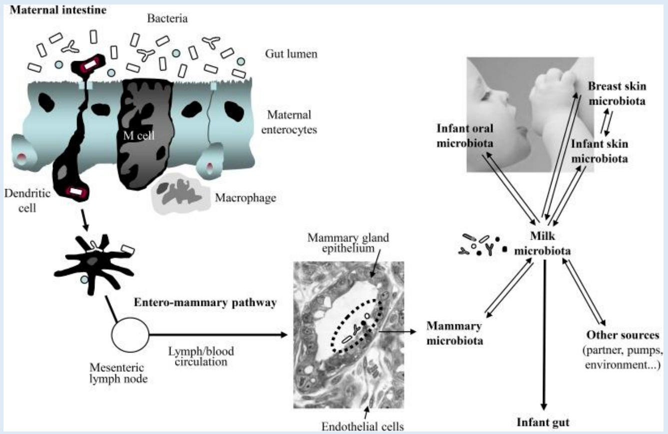
Results

Neonatal Morbidities		
	MOM (n=29)	DM (n=12)
Survival, n (%)	25 (86)	10 (83)
Length of stay, days, mean (S.D.)	104 (64)	89 (37)
DOL at full feeds, mean (S.D.)	28.0 (23.0)	26.0 (20.0)
NEC stage 2+, n (%)	1 (3)	1 (8)
Sepsis, n (%)	1 (3)	0 (0)
ROP stage 3+, n (%)	2 (7)	1 (8)
IVH grade 3+/PVL, n (%)	2 (7)	1 (8)
O_2 at DC, n (%)	9 (31)	7 (58)
CGA at DC, mean (S.D.)	39.8 (8.9)	37.8 (4.9)

Growth Parameters		
	MOM (n=29)	DM (n=12)
Growth velocity, g/kg/day, mean (S.D.)	11.1 (9.8)	12.9 (2.1)
HC growth, cm/wk, mean (S.D.)	0.62 (0.5)	0.72 (0.1)
EUGR, n (%)	9 (31)	7 (58)

A. Rahman, B. Parvez et al. PAS 2017

Human milk is not sterile: Impact of the Microbiome



- Bacteria in breast milk, amniotic fluid, birth canal and maternal skin
- Human milk **oligosaccharides** (HMO): 4 milk types, prevention of pathogen adhesion, modulation of epithelial and immune and cell response, inhibition of TLR-4, **modulating the microbiome**
- Early interaction with commensal microbes is essential for healthy immune development and metabolic programming
- Epidemiological studies have reported associations between C-section delivery and an increased risk of
  - Obesity
  - Asthma
  - Allergies
  - Immune deficiencies

Bacteriological, biochemical, and immunological properties of colostrum and mature milk from mothers of extremely preterm infants. Moles L. J Pediatr Gastroenterol Nutr. 2015 Jan;60(1):120-6.
The origin of human milk bacteria: is there a bacterial entero-mammary pathway during late pregnancy and lactation? Rodríguez JM . Adv Nutr. 2014 Nov 14;5(6):779-84.
Dominguez-Bello, M.G. *et al. Proc. Natl. Acad. Sci. USA* **107**, 11971–11975 (2010).

Growth parameters of ELBW Infants Fed Donor Milk

	Donor Milk	Preterm Formula	Mother's Milk	p
BW (grams)	947±233	957±267	999±259	NS
GA (weeks)	27±2	27±2	27±2	NS
Weight gain (g/kg/day)	17±5*	20±7	19±6	P=0.01
Length gain (cm/kg/week)	1.2±0.8	1±1	0.6±04*	P=0.03
HC increase (cm/week)	0.9±0.9	0.9±0.8	0.8±0.5	NS

RCT of DHM vs preterm formula. Schanler. Peds 2005

	Control	Cream	p
BW (grams)	972 ± 150	969 ± 140	.92
GA (weeks)	27.7 ± 2.1	27.6 ± 1.6	.88
Weight gain (g/kg/day)	12.4 ± 3.9	14.0 ± 2.5	.03
Length gain (cm/week)	0.83 ± 0.41	1.03 ± 0.33	.02
HC increase (cm/week)	0.84 ± 0.22	0.90 ± 0.19	.02

Hair A RCT of human milk cream as a supplement to standard fortification in exclusive human diet. JPeds 2014

Growth patterns of extremely low birth weight infants fed exclusive donor (DM) versus exclusive mother's own breast milk (MOM) until 34 weeks corrected gestational age

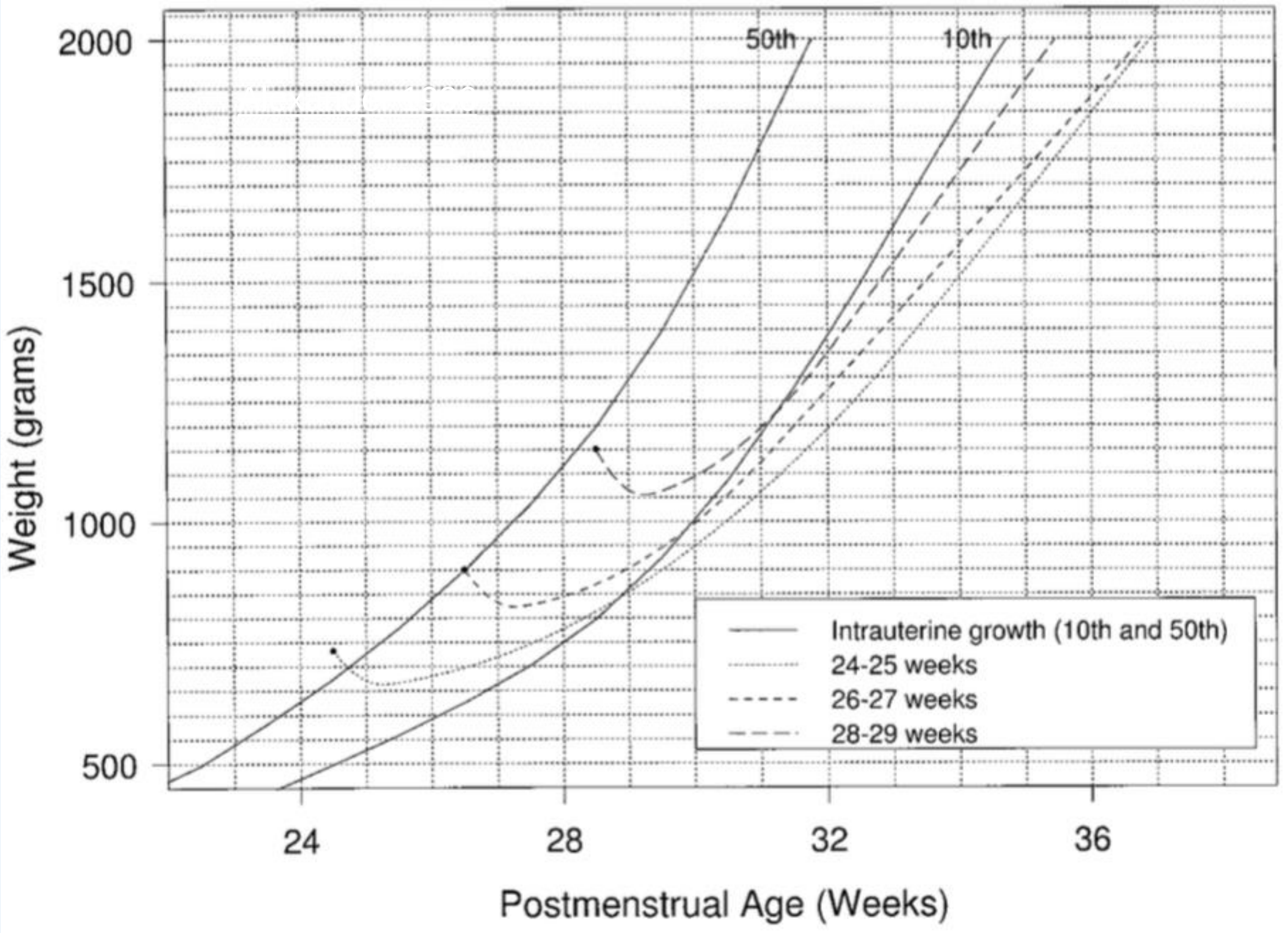
Maternal Characteristics		
	MOM (n=29)	Donor Milk (n=12)
Age, mean (S.D.)	30.5 (6.6)	30.3 (±6.1)
Extreme maternal age, n (%)	10 (35)	3 (25)
African American, n (%)	9 (31)	4 (33)
Preeclampsia, n (%)	3 (10)	5 (42)*
C-section, n (%)	14 (48)	4 (33)
PROM, n (%)	11 (41)	3 (25)
Chorioamnionitis, n (%)	5 (17)	1 (8)
Antenatal Steroids, n (%)	27 (93)	11 (92)
Outborn, n (%)	1 (3)	4 (33)*

*p<0.05

Neonatal Characteristics		
	MOM (n=29)	DM (n=12)
Male sex, n (%)	16 (55)	6 (50)
GA in weeks, mean (S.D.)	25.4 (± 2.0)	25.7 (1.7)
Birth Weight in grams, mean (S.D.)	751 (±161)	742 (207)
SGA, n (%)	2 (7)	1 (8)
Head circumference, cm, mean (S.D.)	22.6 (±1.6)	22.3 (2.2)
5 min APGAR <5, n (%)	11 (41)	3 (25)

A. Rahman, B. Parvez et al. PAS 2017

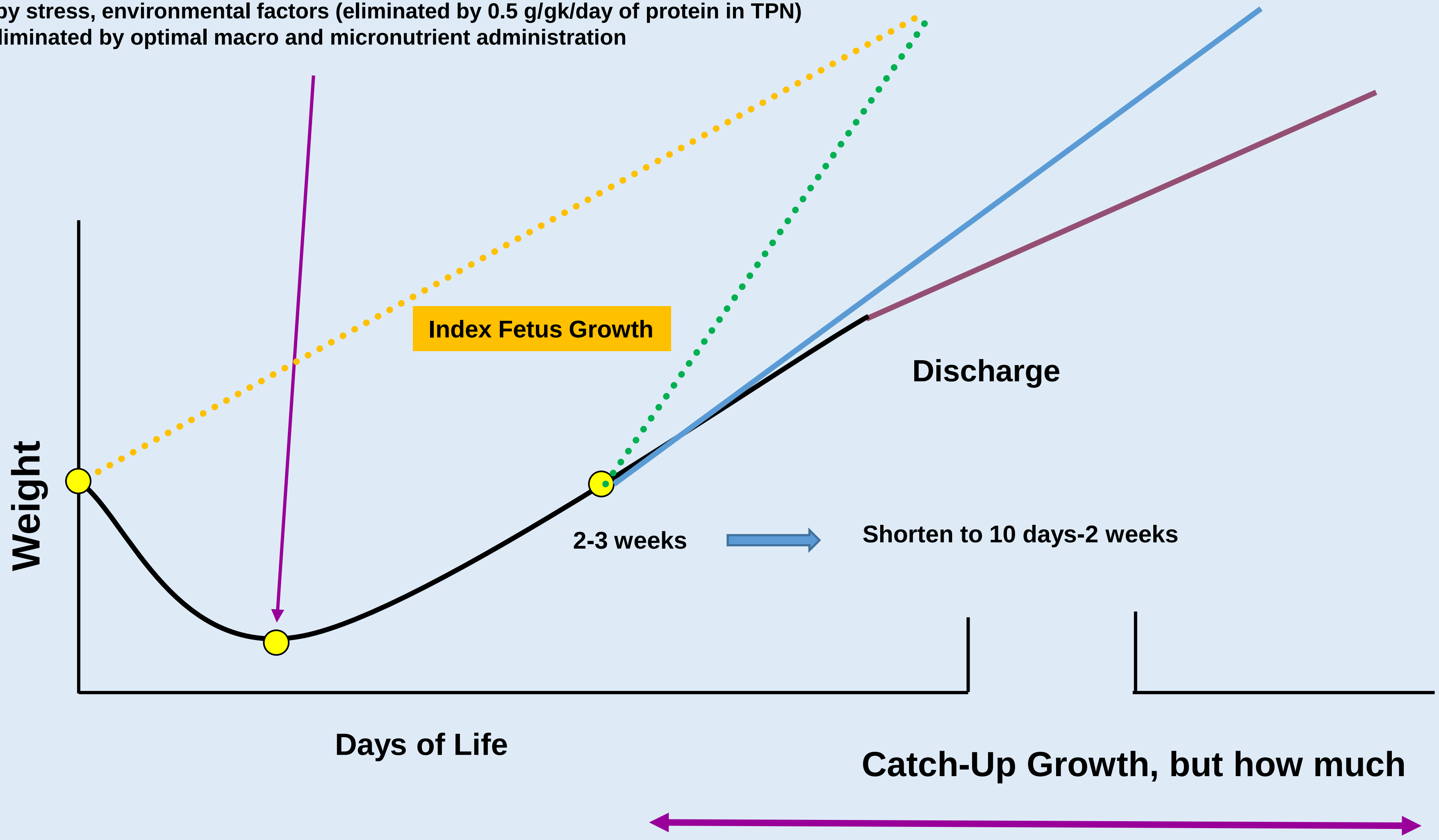
ELBW Infants are at High Risk of EUGR at Discharge



Richard A. Ehrenkranz, et. al. "Longitudinal Growth of Hospitalized Very Low Birth Weight Infants." Pediatrics 104.2 (1999): 280-89.

Infants Growth in NICU and after Discharge

Obligatory ECF loss
Increased metabolic demand (RDS, environmental factors, morbidities)
Catabolic state, triggered by stress, environmental factors (eliminated by 0.5 g/gk/day of protein in TPN)
Caloric/ Nutrient Deficit (Eliminated by optimal macro and micronutrient administration



Modified from: Adamkin DH. Feeding PT Infant in Perinatal Nutrition: Optimizing Infant Health and Development. Marcel Dekker, 2005

Fenton Growth Chart 2013