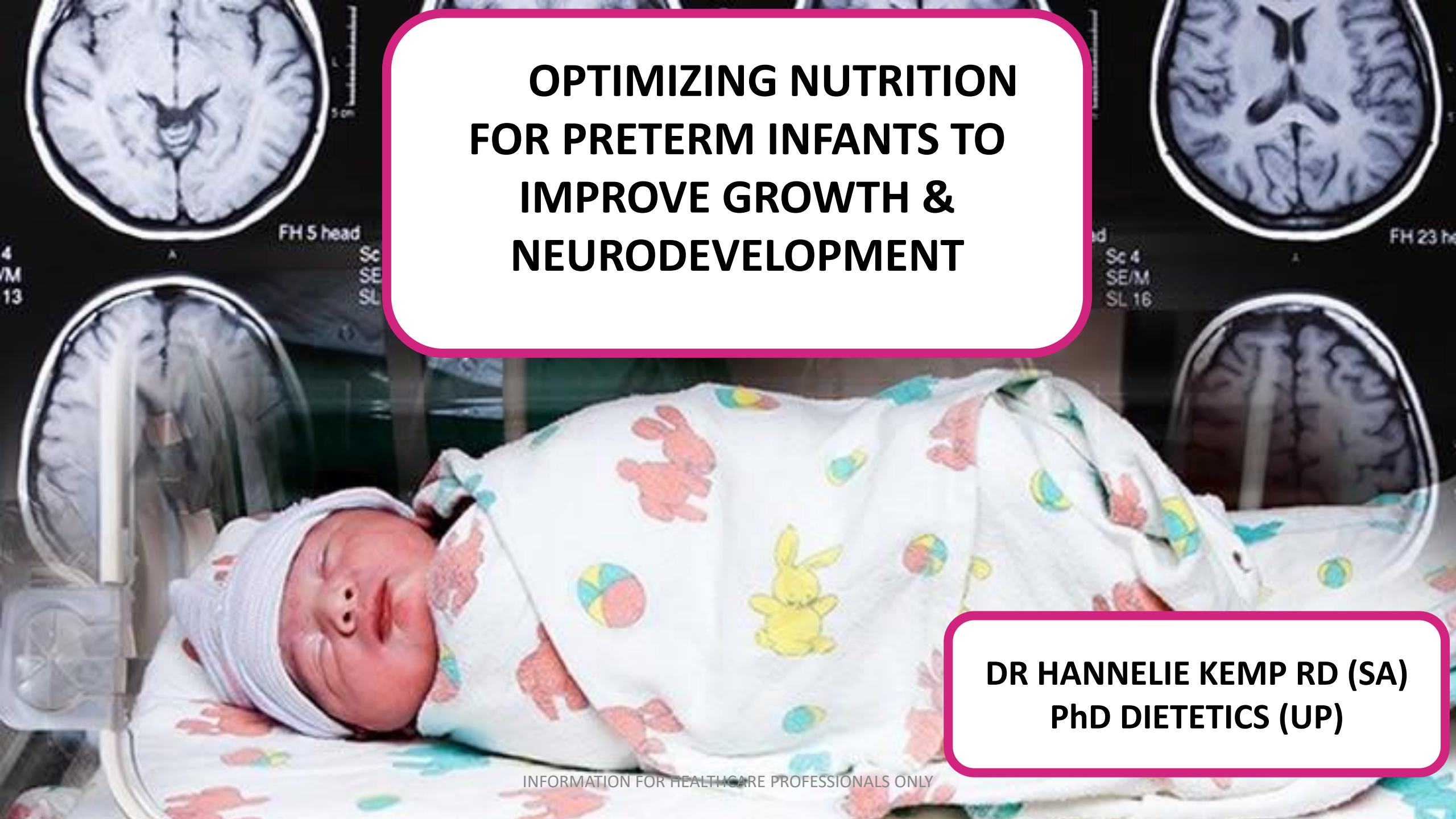

OPTIMIZING NUTRITION FOR PRETERM INFANTS TO IMPROVE GROWTH & NEURODEVELOPMENT

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NUTRITION FOR PRETERM INFANTS

CONFLICT OF INTEREST

I have acted in an advisory capacity/written articles/medical copywriting/gave lectures/received honoraria for/from:

- Both companies with human milk fortifiers on the SA market:
  - Nestlè South Africa PTY (Ltd)
  - Sanulac
- Companies with parenteral nutrition on the SA market:
  - Baxter
  - Fresenius Kabi

NUTRITION FOR PRETERM INFANTS

OUTLINE OF TODAY'S TALK

- **BACKGROUND:**
  - **Preterm birth = nutritional emergency**
    - Abrupt end of nutrition via placenta
    - Rapid growth during 3rd trimester (Example: brain)
    - Born with poor nutrient reserves
- **GOALS OF NUTRITION SUPPORT:**
  - What should we aim for?
  - What is optimal growth?
- **OTIMIZING NUTRITION SUPPORT:**
  - Stages of nutrition support
    - Parenteral nutrition
    - Enteral nutrition
    - Early nutrition
  - **Role of nutrition in neurodevelopment**
    - Link between growth & neurodevelopment
    - Focus: unique roll of breast milk
- **CONCLUSION**

NUTRITION FOR PRETERM INFANTS: Background

NUTRITIONAL EMERGENCY

"Preterm birth = not only medical emergency but also nutritional emergency!" *(Corpeleijn, 2011)*

1.) Abrupt end of placental supply of nutrients

- **Very high accretion rates** in late gestation e.g., up to 80% of Ca, Phos deposited in bone tissue in 3rd trimester
- **We** have to take over the role of the placenta (see next slide)

2.) Rapid foetal growth during the 3rd trimester

- See example of brain growth (see later slides)

3.) Preterm born with poor nutrient reserves (see later slides)

- Deficits of: Energy, protein and micronutrients
- Deficits ↑ as GA and birth weight ↓

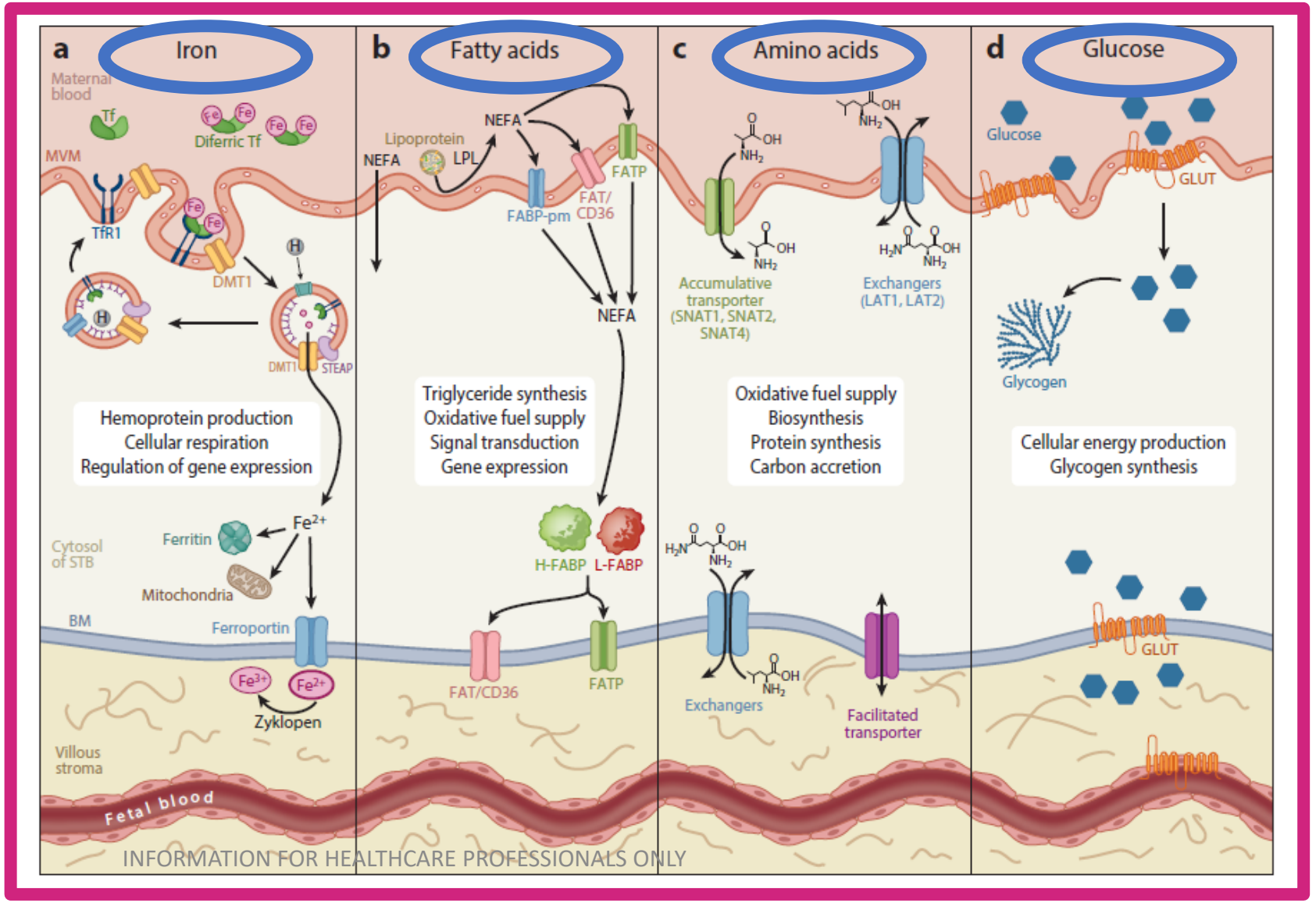
Add cumulative nutritive deficits experienced after birth **=**

Nutritional emergency!

If left untreated: serious detrimental consequences, both short- and long term!

PRETERM BIRTH: Nutritional Emergency

1.) ABRUPT END OF NUTRITION VIA PLACENTA ***(O'Brien, 2022)***



PRETERM BIRTH: Nutritional Emergency

2.) RAPID GROWTH DURING 3RD TRIMESTER

Brain as an example: critical growth period

- Extensive internal growth and differentiation during late 2nd and 3rd trimester

A few interesting facts: *(Ramel & Georgieff, 2014)*

- **By 25 weeks**: Brain resembles a "Coffee bean": bi-lobed and smooth without sulci or gyri

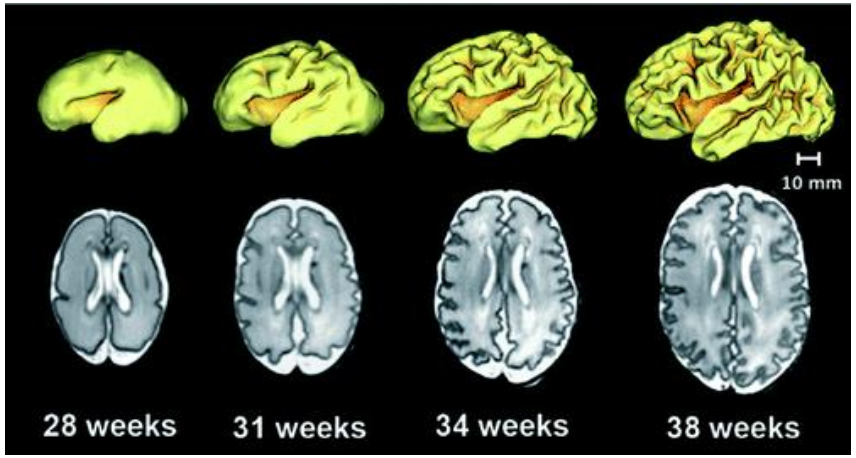
- **At 40 weeks**: Brain resembles a "Walnut": bi-lobed with extensive sulcation and gyration

PRETERM BIRTH: Nutritional Emergency

2.) RAPID GROWTH DURING 3RD TRIMESTER

A few more interesting facts on brain growth:

- **From 25 to 37 weeks:** *(Clouchoux et al 2012)*
  - Cerebral volume increase by 230%
  - Cerebellar volume increase by 384%
- **After birth:** *(Steiner 2019)*
  - As many as 700 000 synapses per second formed



PRETERM BIRTH: Nutritional Emergency

3.) BORN WITH POOR NUTRIENT RESERVES

- **Example: Preterm infant weighing (AGA)1000g**

(Mahan & Escott, 2008)

- Fat constitutes only 1% of total body weight
- Protein 8%
- Glycogen and fat reserve equivalent to 110kcal/kg
- Basal metabolic needs approximately 35-60kcal/kg/day → Infant will rapidly run out of glucose and fat → **breakdown of protein for energy (we do not want this!!)**
- Increased basal metabolic rates in SGA infants
  - **Thus: the shortest depletion times in smallest infants with IUGR**

GOALS OF NUTRITION SUPPORT

WHAT SHOULD WE AIM FOR?

- **American Academy of Pediatrics:**

"to **provide nutrients** to approximate the **rate of growth** and **composition** of weight gain for a normal foetus of the same postmenstrual age and to maintain **normal concentrations** of **blood** and **tissue nutrients**" *(AAP 2014)*

- **Consensus statement (Italian group):**

"to **not lose more than 1 SD** for **weight** and **HC** from birth to D/C from hospital" *(Moro et al 2015)*

  - HC growth NB for neurodevelopment

GOALS OF NUTRITION SUPPORT

WHAT SHOULD WE AIM FOR?

American Academy of Pediatrics: (*AAP, 2014)*

- Growth at similar rates as would have occurred in-utero: **but** can we achieve it?
- **For example:**
  - 24/40 prem would have to double birth weight by 30/40 and ↑ birthweight > 5times by 40/40 to match foetal growth *(Harding, 2017)*
- Hardly achieved in practice!

GOALS OF NUTRITION SUPPORT

WHAT IS OPTIMAL GROWTH?

ESPGHAN (2022):

"Improving short & long-term functional outcome:
Balance between:

- **well-documented neurocognitive risks** of **nutrient deficiencies** and **slow growth** **versus**
- **theoretical risks of adverse metabolic programming in later life** from **rapid catch-up growth"** *(Note: not all authors agree that metabolic programming applies to preterm infants)*

GOALS OF NUTRITION SUPPORT

WHAT IS OPTIMAL GROWTH?

ESPGHAN (2022) Continue:

"Postnatal **growth trajectories** of **each infant** must be followed and evaluated to **ensure nutrition is adequate**.

- **After initial weight** aim to regain birth weight → **growth along a target centile** → gradual transition to corresponding birth centile on WHO chart within weeks or months of post term"

- **Fenton (2024) "No specific percentile should be set as a growth goal; rather, individual variability should be expected. Aim for growth approximately parallel to growth chart curve"**

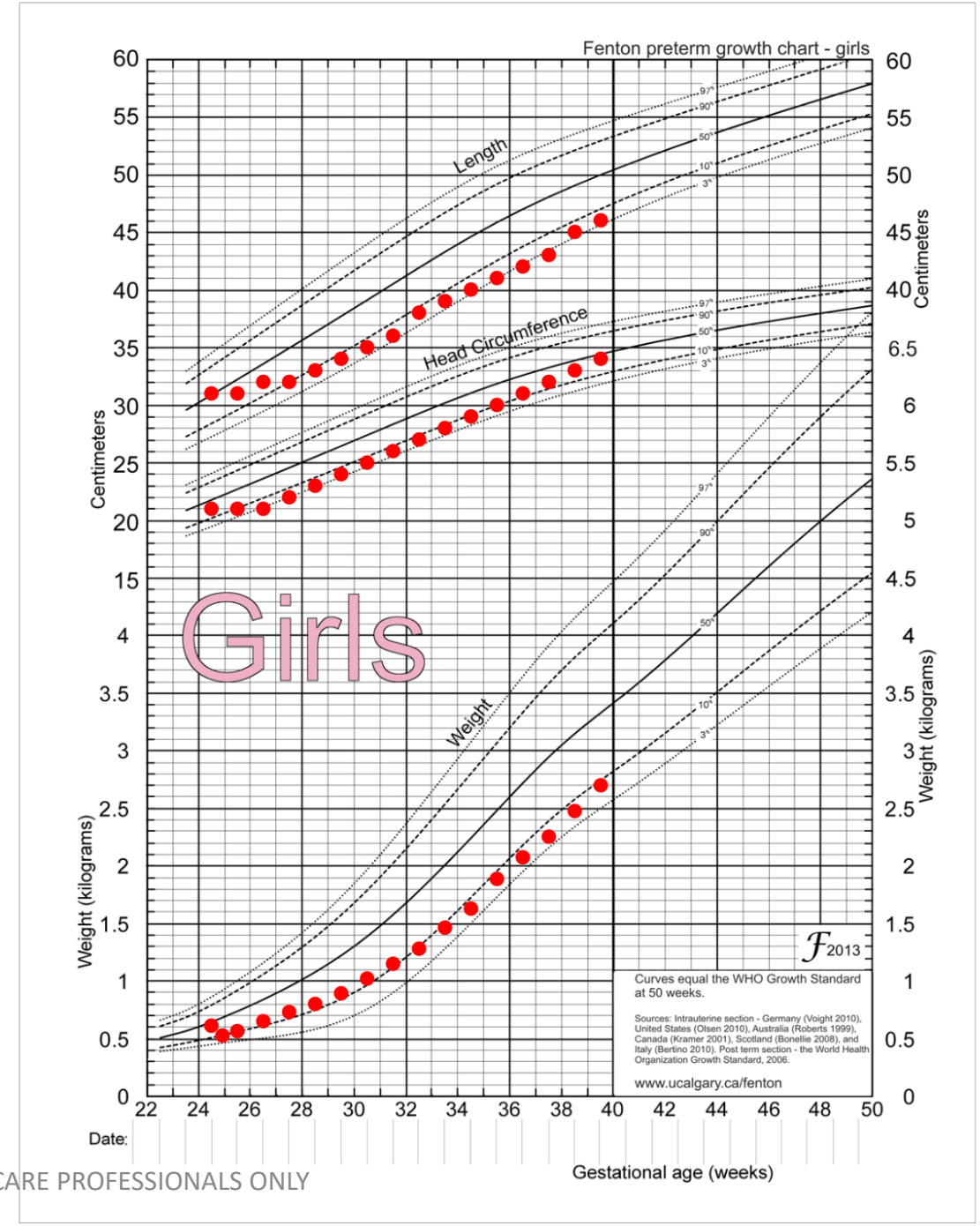
- **NB Growth not always "back at birth centile"** Next two slides with permission from the author *(Fenton et al, Clin Perinatol 2022)*

Growth chart courtesy of Prof Fenton *(Fenton et al, Clin Perinatol 2022)*

?

24/40 Female

Appropriate growth?

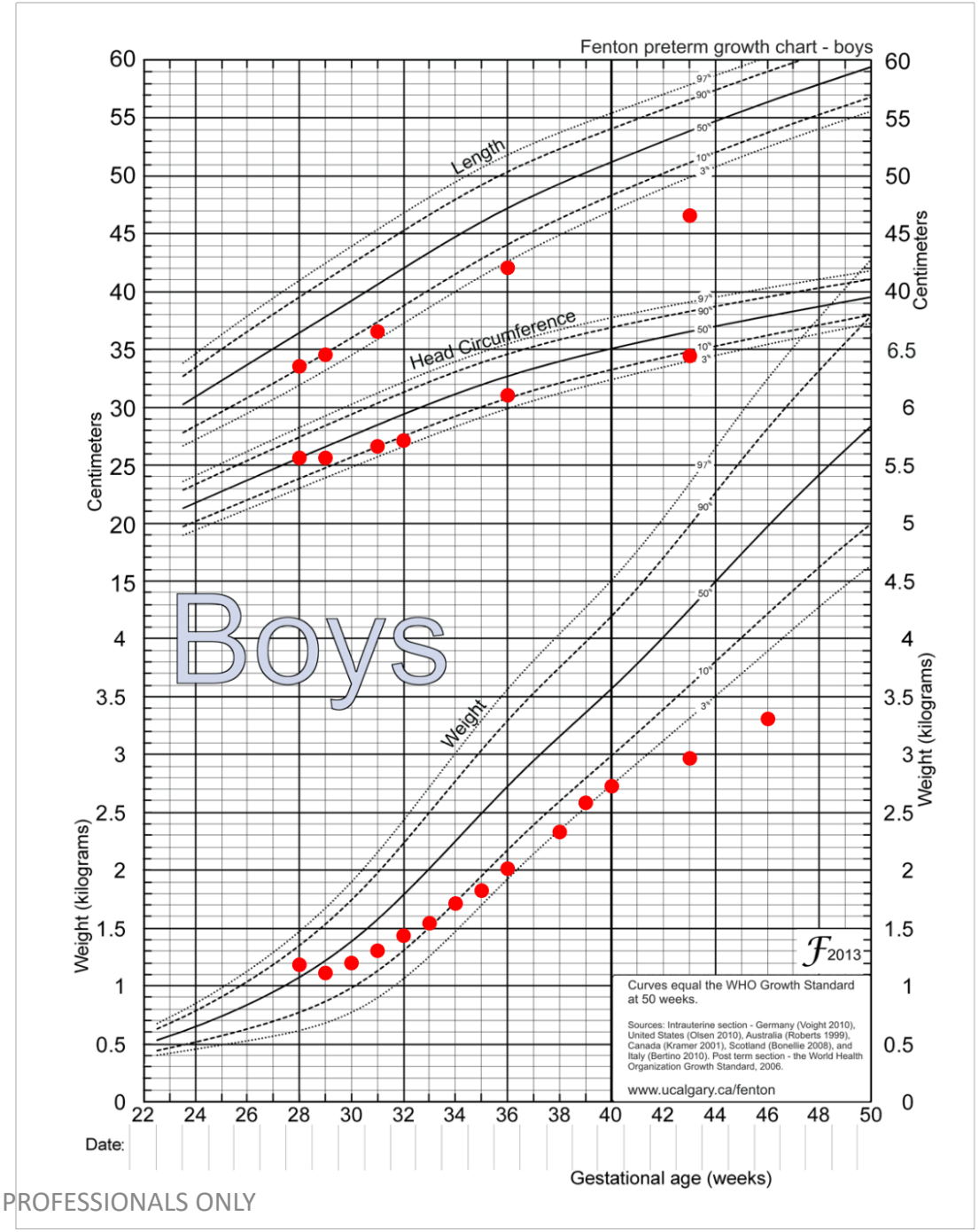


Growth chart courtesy of Prof Fenton *(Fenton et al, Clin Perinatol 2022)*

?

28/40 Male

Appropriate growth?



OPTIMIZING NUTRITION SUPPORT

STAGES OF NUTRITION SUPPORT

(Adapted from Sue et al, 2014)

Acute stage

- Early PN (IV fluid only if PN not indicated)
- Oral administration of colostrum
- Enteral feeds to start as soon as possible

Building feeds

- If on PN: ↓PN and ↑ enteral feeds
- Nutritional feeds – HMF of breastmilk
- Vitamin & Mineral supplements

Growing stage

- Full enteral feeds – HMF of breastmilk
- Preparation for discharge

Progression depends on many factors including GA, Birth wt, Co-morbidities, Feeding tolerance, etc

OPTIMIZING NUTRITION SUPPORT

PARENTERAL NUTRITION

- **2 Critical timepoints for PN:**
  - **1st week of life**
  - **Transition PN to EN:** high risk for poor growth due to inadequate intake
- **PN is a life-saving therapy for high-risk neonates, but also carries a risk…**
  - **Preterm infants are "metabolically vulnerable" especially in the first few days of life:**
    - **NEON trial** *(Uthaya, 2021)* "50% developed at least one of several biochemical abnormalities (**↑glucose, ↑TG, ↑S-Ur**) that are associated with increased mortality and long-term neurodevelopmental impairment"
    - **Neonatal Refeeding Syndrome**
  - **Complications of long term PN e.g., IFALD, MBD**

OPTIMIZING NUTRITION SUPPORT

PARENTERAL NUTRITION

PN Indications in preterm infants

- PN needed where significant weight loss and E and protein deficits common:
  - ELBW prems
  - GA < 30/40 (**NICE 2020:** < 31wk, start immediately)
  - PN during **first week of life** shown to improve weight loss and deficits
- PN helpful when fluid restricted – may improve time to regain birth weight and improve nutritional intake
- Risk-benefit ratio less clear for larger, more mature infants ≥ 32 weeks GA (**NICE 2020:** 31wk +, start @ 72h if insufficient EN progress)

OPTIMIZING NUTRITION SUPPORT

PARENTERAL NUTRITION

PN Indications in preterm infants (Continue)

- Other **NICE (2020)** guidelines to start:
  - If unlikely to establish EN e.g. congenital GIT conditions, critically ill
  - If EN stopped and unlikely to be started within 48
  - If EN has been stopped for 24h and unlikely to make sufficient progress with EN within next 48h

- **Guidelines on PN recommendations:**
  - ESPGHAN (2018)
  - ASPEN (2015 and 2023)
  - AAP (2020)
  - NICE (2020)

OPTIMIZING NUTRITION SUPPORT

ENTERAL NUTRITION

Enteral nutrition (EN) – always preferred above PN

- **Human milk** - preferred feed for all infants, including preterm infants.
  - **Numerous advantages…..**
    - Dependent on dose and duration, include:
      - ↓ NEC
      - ↓ Late-onset sepsis
      - ↓ Retinopathy
      - Better feeding tolerance
      - Improved neurodevelopmental outcomes (see later)
  - **Mother's own milk 1st choice**
    - Donor milk 2nd choice – if preterm donor milk available: preferred over mature donor milk
    - Preterm formula 3rd choice

Guidelines on EN recommendations: ESPGHAN (2022) – see next slides

OPTIMIZING NUTRITION SUPPORT

ENTERAL NUTRITION

- **Background to ESPGHAN 2022 Position Paper *(Embleton et al, JPGN 2023)***
- Consensus document
  - >90% consensus reached for LOE and GOR (SDC 1)
- Indicators of best practice only
- To be adopted with consideration of **local contexts and individual infants**
- For preterm infants with **birth weight < 1800g**
  - For moderate to late prems > 1800g: Separate ESPGHAN guideline *(Lapilonne et al, 2019)*
- **Strong support for the use of human milk – especially MOM**
  - Human milk – values used (SDS Table 1) (Not systematic review/meta-analysis)

Fortification – next slide

OPTIMIZING NUTRITION SUPPORT

ENTERAL NUTRITION

ESPGHAN (2022):

- **Multi-component** fortifiers
- Insufficient evidence to recommend routine use of human milk-derived fortifiers (not available in our region)
- Start when enteral intakes **@ 40 to 100mL/kg/day**
- **Donor milk** may require higher levels of fortification than MOM
- Optimal strategy uncertain (standard vs adjustable vs target)
- **Also separate document just on HMF:**

ESPGHAN Committee of Nutrition (CoN) Position Paper on Enteral Nutrition for Preterm Infants: Breast milk fortification *(Fusch et al, February 2022)*

FROM THEORY TO PRACTICE:
ESPGHAN (2022) REQUIREMENTS

Example of **1kg infant** (kcal/kg = kcal/d) with human milk*
@ **150mL/kg**
NO FORTIFIER OR SUPPLEMENTS ADDED

	Requirement	150mL HM
Energy (kcal/day)	115-140 (160)	**98-113**
Protein (g/day)	3.5-4.0 (4.5)	**1.8-2.3**
Fat (g/day)	4.8-8.1	**4.5-5.3**
CHO (g/day)	11-15 (17)	**8.9-10.1**
Protein:Energy ratio (g/100kcal)	2.8-3.6	**1.6-2.3**
Calcium (mmoL/day)	3.0-5.0	**0.9-1.1**
Phosphorous (mmoL/day)	2.2-3.7	**0.6-0.8**

***Human milk values used per 100mL: 65-75kcal; 1.2-1.5g protein; 3.0-3.5g fat; 5.7-6.7g CHO; 0.6-0.75mmoL Ca; 0.4-0.55mmoL Phos**
(ESPGHAN 2022; SDC Table 1, Day 7 to 28 of life)

FROM THEORY TO PRACTICE:
MEETING ESPGHAN (2022) REQUIREMENTS

Example of **1kg infant** (kcal/kg = kcal/d) with human milk* @ **200mL/kg**
NO FORTIFIER OR SUPPLEMENTS ADDED

	Requirement	200mL HM
Energy (kcal/day)	115-140 (160)	130-150
Protein (g/day)	3.5-4.0 (4.5)	**2.4-3.0**
Fat (g/day)	4.8-8.1	6.0-7.0
CHO (g/day)	11-15 (17)	11.4-13.4
Protein:Energy ratio (g/100kcal)	2.8-3.6	**1.6-2.3**
Calcium (mmoL/day)	3.0-5.0	**1.2-1.5**
Phosphorous (mmoL/day)	2.2-3.7	**0.8-1.1**

***Human milk values used per 100mL: 65-75kcal; 1.2-1.5g protein; 3.0-3.5g fat; 5.7-6.7g CHO; 0.6-0.75mmoL Ca; 0.4-0.55mmoL Phos**
(ESPGHAN 2022; SDC Table 1, Day 7 to 28 of life)

FROM THEORY TO PRACTICE:
MEETING ESPGHAN (2022) REQUIREMENTS

Example of **1kg infant** (kcal/kg = kcal/d) with human milk*
@ **150mL/kg**
MCT OIL ADDED

	Requirement	150mL HM
Energy (kcal/day)	115-140 (160)	**115-130**
Protein (g/day)	3.5-4.0 (4.5)	**1.8-2.3**
Fat (g/day)	4.8-8.1	**6.4-7.2**
CHO (g/day)	11-15 (17)	**8.9-10.1**
Protein:Energy ratio (g/100kcal)	2.8-3.6	**1.4-2.0**
Calcium (mmoL/day)	3.0-5.0	**0.9-1.1**
Phosphorous (mmoL/day)	2.2-3.7	**0.6-0.8**

***Human milk values as before**
****** **0.5mL MCT oil added to 4 feeds per day = 2mL/day added**

FROM THEORY TO PRACTICE:
MEETING ESPGHAN (2022) REQUIREMENTS

Example of **1kg infant** (kcal/kg = kcal/d) with human milk*
@ **150mL/kg**
HUMAN MILK FORTIFIER ADDED

	Requirement	150mL HM
Energy (kcal/day)	115-140 (160)	**122-137**
Protein (g/day)	3.5-4.0 (4.5)	**3.6-4.1**
Fat (g/day)	4.8-8.1	**6.3-7.1**
CHO (g/day)	11-15 (17)	**11.3-12.5**
Protein:Energy ratio (g/100kcal)	2.8-3.6	**2.6-3.4**
Calcium (mmoL/day)	3.0-5.0	**4.0-4.2**
Phosphorous (mmoL/day)	2.2-3.7	**2.8-3.0**

***Human milk values as before**
****Standard fortification: 6g/day (average values of 2 HMF available in SA)**

OPTIMIZING NUTRITION SUPPORT

EARLY NUTRITION

Examples of studies on nutrient intake in the first few weeks of life:

- Higher energy and protein intake in VLBW infants: *(Shim, 2014)*
  - Improved language scores at 18 months CA
- Higher energy and lipid intake in infants < 28 GA: *(Dit Trolli, 2012)*
  - Increased developmental quotient (DQ) at 1 year CA
- Higher energy and lipid intake in infants born ≤ 30 GA : *(Beauport, 2017)*
  - Lower incidence of brain lesions and dysmaturation (MRI) at term equivalent age (MRI)

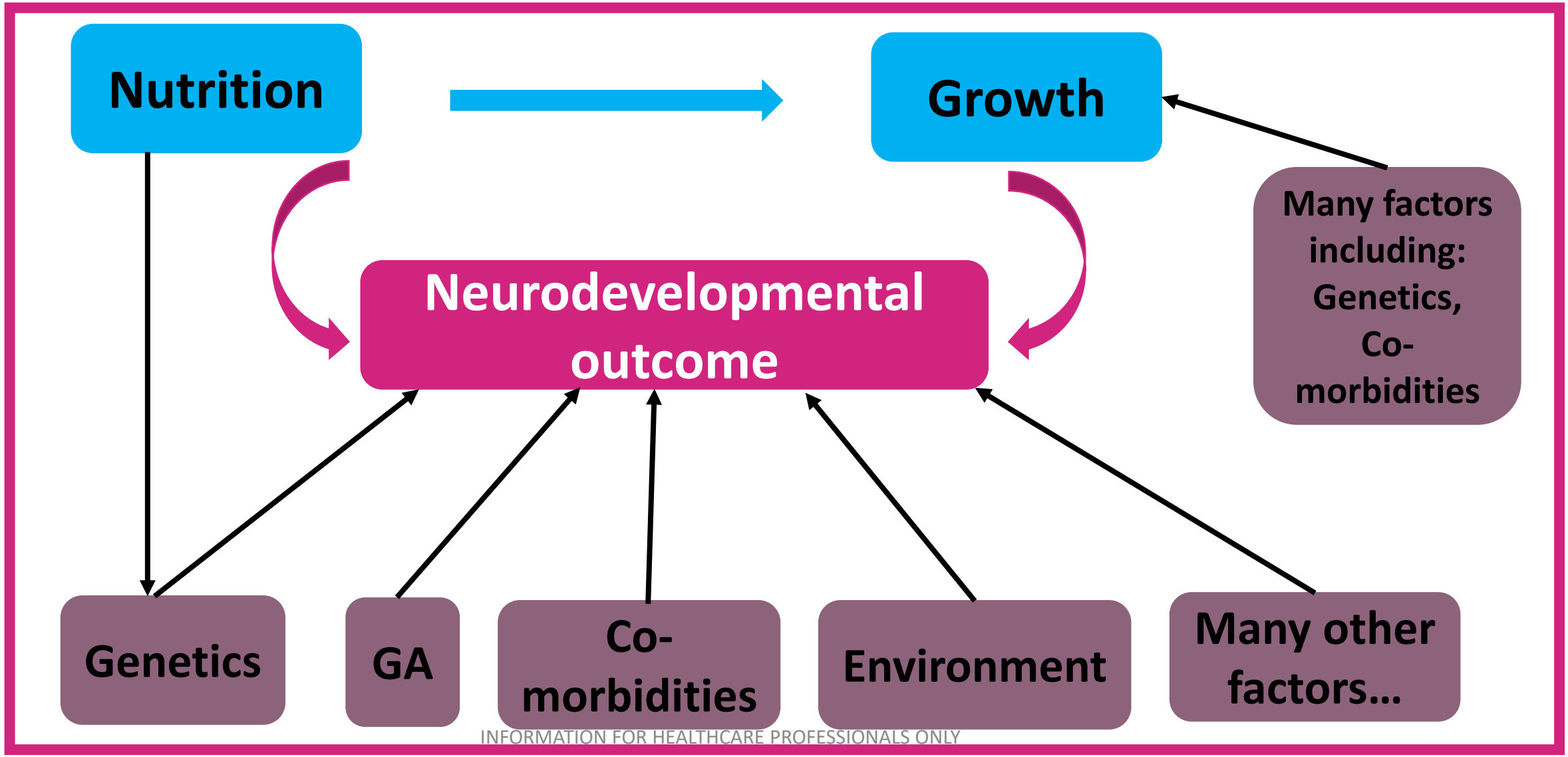
- **Parenteral vs Enteral nutrition**
  - **Better effects enteral**

OPTIMIZING NUTRITION SUPPORT

LINK BETWEEN GROWTH & NEURODEVELOPMENT

- **Numerous studies showing associations with weight, length and HC gain:**
  - **Ehrenkranz et al (Pediatrics, 2006) well-known study:**
    - "Growth velocity during an ELBW infant's NICU hospitalization exerts a significant, and possibly independent, effect on neurodevelopmental and growth outcomes at 18 to 22 months' corrected age."
  - **Belfort et al (Pediatrics, 2011):**
    - In preterm infants with GA <33/40: Greater weight and BMI gain to term-equivalent age also associated with better neurodevelopmental outcomes at 18 months of age

OPTIMIZING NUTRITION: Link between growth and neurodevelopment



OPTIMIZING NUTRITION SUPPORT

ROLE OF NUTRITION IN NEURODEVELOPMENT

- **Role of nutrition in brain growth:** *(Georgieff 2022; Prado 2014)*
  - **Five key neurodevelopmental processes:**
    - Neuron proliferation
    - Axon and dendrite growth
    - Synapse formation, pruning and function
    - Myelination
    - Neuron apoptosis
- **Nutritional factors: independent determinants of lifelong neurodevelopment and intellectual performance** *(Agostoni 2013)*
- **Many nutrients/nutritive factors may play a role**
  - Not acting in isolation, even though discussed as such
  - “Critical periods” e.g., Iron and Iodine intake

OPTIMIZING NUTRITION SUPPORT

ROLE OF BREASTMILK IN NEURODEVELOPMENT

- **Breast milk – specifically mothers own milk (MOM)**
- **"Apparent breastmilk paradox"** *(Rozè et al 2012)*
  - Data from EPIPAGE and LIFT studies: very preterm infants (some SGA)
  - **Despite sub-optimal initial weight gain: better neurodevelopment in breastfed infants**
- **Effect of breastmilk is well known:**
  - Positive link between maternal breast milk and neurodevelopment in preterm infants that may last beyond infancy
- **Neuroprotective**
  - e.g., antioxidant properties of lactoferrin and glycoproteins
- **Neurotrophic**
  - e.g., LCPUFA's
- Mothers own milk vs Donor vs Preterm formula.

OPTIMIZING NUTRITION SUPPORT

ROLE OF BREASTMILK IN NEURODEVELOPMENT

- **Possible factors in breastmilk/associated with breastfeeding**
  - Protein including specific amino acids: Taurine, Glutamine
  - Fatty acids: **Long chain poly-unsaturated fatty acids (LCPUFA's),** sphingomyelin
  - Probiotics and **Human milk oligosaccharides (HMO's)**
  - Vitamins and minerals e.g., Vitamin A, Fe (high bioavailability in human milk)
    - E.g., Fe is important for neural myelination and neurotransmitter function
  - Lactoferrin, glycoproteins, growth hormones etc
  - KMC and mother-infant bonding
- **To be discussed today**

OPTIMIZING NUTRITION SUPPORT

ROLE OF BREAST MILK IN NEURODEVELOPMENT: LCPUFA's

- **Two important LCPUFA's: DHA and ARA**
  - Synthesized from precursor fatty acids (EFA: ω-3 and ω-6)
  - But ω-3 → DHA slow process in humans
  - Membrane PUFA more responsive to dietary DHA than to ω-3
- **Brain is one of the organs richest in lipids**
  - DHA and ARA found in abundance in the brain
  - DHA (also visual activity): higher dosages to be added to all infant and follow-on formulas (European regulation 2016)
  - Koletzko et al (2020): ARA as well
  - **Breast milk always contains both DHA and ARA**
  - **NB! MCT oil does not contain any EFA or LCPUFA's!**

OPTIMIZING NUTRITION SUPPORT

ROLE OF BREASTMILK IN NEURODEVELOPMENT: LCPUFA's

- **More specific to preterm infants:**
  - 3rd Trimester: Placenta **actively** and **selectively** chose **DHA** and **ARA** from the mother for delivery to the foetus *(Schneider & Garcia-Rodenas 2017)*
  - **Prems high risk of LCPUFA deficiency** – ↓supply via placenta, ↑demand, very low fat stores, impaired absorption etc
    - Lipase in breast milk improves absorption
    - DBM: Pasteurisation, freeze-thaw cycles, multiple container changes, prolonged storage times reduce bioactivity – including ↓ lipase levels

OPTIMIZING NUTRITION SUPPORT

ROLE OF BREASTMILK IN NEURODEVELOPMENT: LCPUFA's

- **LCPUFA's and Cognitive function:**
- Large body of evidence linking early LCPUFA intake and cognitive benefits in preterm infants
- **Optimal LCPUFA?**
  - Dosage
  - Combinations and ratios
  - Oil sources
  - Timing and length of intervention
- **DHA** (but not ARA) **in human milk is dependent on mother's intake** – promote **fatty fish** intake! (Pregnant and BF moms)

OPTIMIZING NUTRITION SUPPORT

ROLE OF BREASTMILK IN NEURODEVELOPMENT: HMO'S

HMO's:

- Bioactive factors, several structurally diverse unconjugated glycans – unique to human milk
- Prebiotic action but "more than just food for bugs" *(Bode 2012)*
- Possible role in "Gut-brain-axis" (GBA)
  - GBA is a mediator connecting the emotional and cognitive areas of the brain to the gut
  - Gut probiotics may be a source of neurotransmitters *(Muhammad et al 2022)*
- Parallel early developmental window pre- and postnatally for gut microbiota and nervous system

OPTIMIZING NUTRITION SUPPORT

ROLE OF BREASTMILK IN NEURODEVELOPMENT: HMO'S

HMO's (Continue)

- Sialyted HMO's: **source of sialic acid**

(Jantscher-Krenn & Bode 2012)

  - Incorporated in gangliosides and glycoproteins
  - Associated with higher learning ability
  - Amount of sialic acid derived from HMO's 2 t0 3-fold higher than those derived from human milk glycoproteins

- NB Fructo-oligosaccharides (FOS) and Galacto-oligosaccharides (GOS):
  - not naturally found in human milk
  - not sialyted

NUTRITION FOR PRETERM INFANTS: Conclusion

FROM THEORY TO PRACTICE

- **PN:** make sure EFA requirements are met
- Encourage **MOM** as **1st** feeding choice
- **Donor milk (DBM)** as **2nd** feeding choice
  - If available use preterm DBM or from smallest GA for most immature/smallest baby
  - DBM "bridge" until full feeds of MOM available (AAP 2021)
- **Fortify** both MOM and DBM with multi-nutrient fortifiers
  - Multi-nutrient fortifiers NB source of nutrients for brain development e.g., LCPUFA's, Fe
  - BUT no EFA, Fe etc in MCT oil or in protein supplements
  - If not available: consider fortifying with preterm formula
- Preterm formula as **3rd** feeding choice
- Vitamin and mineral supplements

NUTRITION FOR PRETERM INFANTS: Conclusion

FROM THEORY TO PRACTICE

- Encourage pregnant and BF mom to eat fatty fish
- Monitor growth – **not only weight, but also HC and L**
- **Post-discharge nutritional care**
  - Encourage **continued breastfeeding** after discharge from hospital
  - Supplementation of vitamins and minerals to continue post-discharge
  - Continue to monitor growth and neurodevelopment – act timeously!!

"Use nature to nurture!" *(Ottolini 2020)*

THANK YOU!