Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

State of the Art: Precision Nutrition in Preterm Infants

Overview

Unique from term infants, preterm infants' enteral nutrition is not self-regulated. Feeding occurs according to a timed schedule, with nutrient intake and feeding volume determined by the neonatal staff, while baby is required to metabolize what is fed. **Christoph Fusch, MD, PhD**, discusses evidence that reveals how to measure and strategically determine micro- and macronutrient needs for preterm neonates. He reviews the impact of balanced nutrient intake and nutritional research studies in preterm infants on clinical outcomes, as well as the significance of applying postnatal growth trajectories and optimal nutrition needs of preterm infants. Although the gold standard, mother's breast milk can vary, and may not provide adequate nutrients for essential growth and neurodevelopment needed in preterm infants. Precision nutrition allows the neonatal staff to adjust nutritional content—including the appropriate amount of proteins, carbohydrates, and fat to result in optimal growth and development—according to individual preterm needs.

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, allergists, and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Explain how nutritional needs vary among preterm and term infants
- Describe the clinical outcomes from nutrient research studies in preterm infants
- Develop individual postnatal growth trajectories for preterm infants to reduce the risk of postnatal growth retardation
- Apply current recommendations based on nutrient research studies for the clinical management of preterm infants.

Faculty

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Christoph Fusch, MD, PhD, FRCPC

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Consultant	Abbott, Baxter, Mead Johnson Nutrition, Nestlé, Nutricia – clinical area: nutrition and growth Hipp – clinical area: preterm formula
Speakers Bureau	Abbott, Baxter, Fresenius, Heinen & Lowenstein, Humana, Ikaria, Mead Johnson Nutrition, Medela, Milupa, Nestlé, Nutricia, Prolacta Bioscience – clinical area: nutrition and growth Hamilton Medical – clinical area: ventilation and respiratory support HiPP – clinical area: preterm formula

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This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on November 22, 2019 and is eligible for credit through November 22, 2021.

Obtain your CE/CME credit at:
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Editor's Note: This is a transcript of an audio webcast presented on November 4, 2019. It has been edited and condensed for clarity.

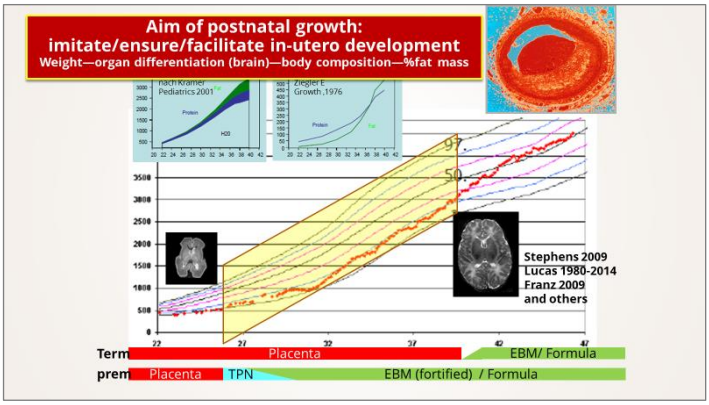
Christoph Fusch: Hello and welcome. I'm quite honored and excited to give this talk about precision medicine in neonatal nutrition. It reflects the work that we have done out of McMaster University during the last couple of years.

Postnatal Growth, Nutrition and Later Outcome

The aim of postnatal growth is to imitate, ensure, and facilitate in utero development. And the American Academy of Pediatrics [2014] recommends that preterm infants achieve, "…rates of growth and composition of weight gain for a normal fetus of the same postmenstrual age and to maintain normal concentration of blood and tissue nutrients." This is one sentence, which is easier said than done.

On this slide [Slide 1], you see that we have to achieve proper growth rates (weight gain), because five-sixth of the body weight of a baby at term is acquired in the neonatal unit [NICU] after it has been born, at the age of 26–27 weeks.

It's not only about weight gain, it's also about achieving the proper organ differentiation. You see the brain of a 24- [left scan] and 42-weeker [right scan]; you see there's a difference in size and volume, but also a difference in structure. We need to give the right nutrients to make that happen.



Slide 1 – Aim of Postnatal Growth

The third thing is that we need to make sure [the baby is] not only growing—gaining weight—but gaining the right quality of weight. You see it in the upper 2 insets that we are talking about achieving the right amount of lean mass and the right amount of fat mass. I would like to draw your attention to that lean mass, which is nearly linearly accreted over the whole fetal life, whereas fat mass starts to be accreted at around 30 weeks, at a different rate than the lean mass.

Postnatal preterm growth patterns are under the control of neonatal staff who modify the infants' nutrient intake. Unlike term babies, preterm infants' feedings are not self-regulated. Feeding volume is determined by neonatal staff. Feeding and nutrient intake occur according to a timed scheduled. The baby has to metabolize nutrition that is being filled

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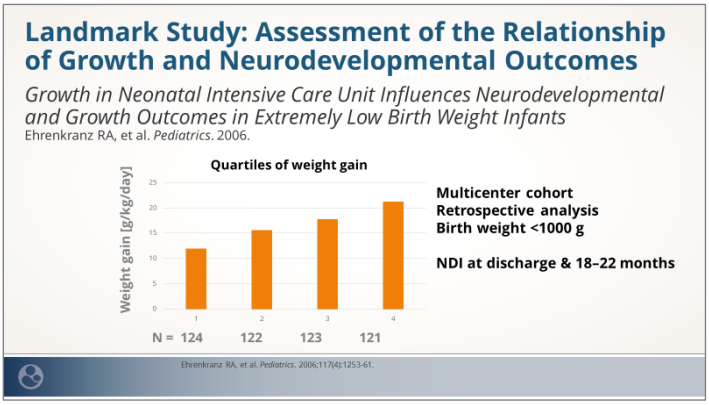
into the body. There's no way to escape, and that's why we need to understand this—the rules of the game of growth.

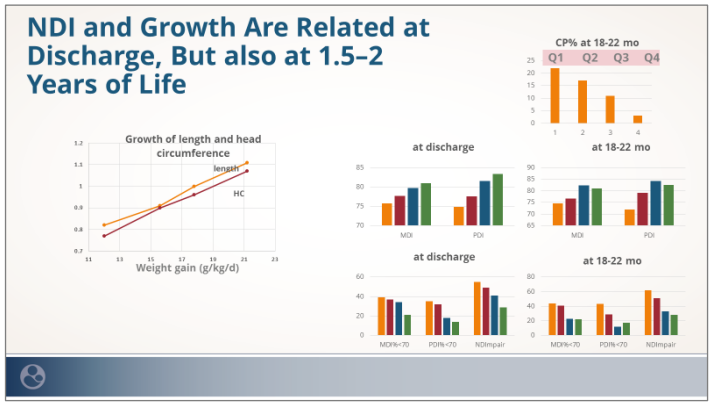
As a landmark study, this relates the relationship of growth to neurodevelopmental outcome by Richard Ehrenkranz, MD.[1] He divided—in this multicenter cohort retrospective analysis in babies below 1000 g—the group into 4 quartiles according to growth. You see [Slide 2] that the lowest growing quartile is around 10–12 g/kg/day, and the highest is around 21 g/kg/day. Then this was correlated to neurodevelopment at discharge and at 18–22 months.



Slide 2 – Landmark Study: Assessment of Relationship of Growth and Neurodevelopmental Outcomes

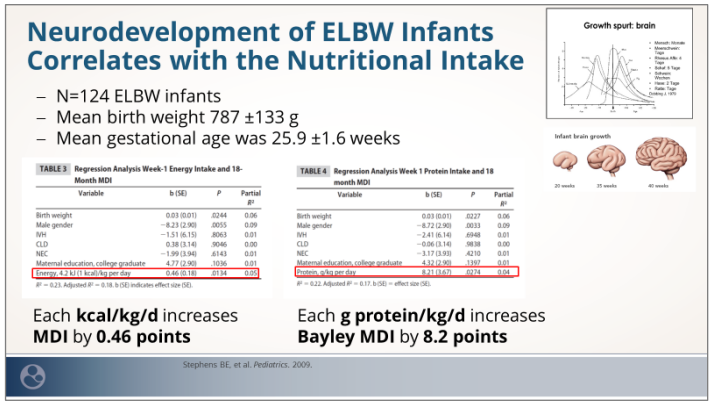
On this slide [Slide 3] you see that the babies do neurodevelopmentally better when they grew better. That is true at discharge, but also at 18–22 months. You see in the upper right [figure], the percentage of cerebral palsy is much lower in babies that grow better compared to babies who grow worse. This is independent from the underlying disease.

This was not an interventional study, and not a randomized study, but just observational.



Slide 3 – NDI and Growth Are Related at Discharge, But Also at 1.5–2 Years of Life

There are more data showing that neurodevelopment of [extremely low-birth-weight] ELBW infants correlates with nutritional intake. This is a study of Bonnie Stephens, MD,[2] [Slide 4] that shows each kcal/kg/d you can increase during the first week of life, increases the [Mental Development Index] MDI by 0.46 points. Each gram protein/kg/d increases the MDI at 8.2 points. This is about nutrient intake in the first week of life.



Slide 4 – Neurodevelopment of ELBW Infants Correlates With the Nutritional Intake

There's a correlation between intake and neurodevelopmental outcome. The **effect size of nutritional intervention is probably in the same range as levels of classical procedures and strategies applied during the "intensive" intensive-care period of a preterm** baby, like giving ventilatory support.

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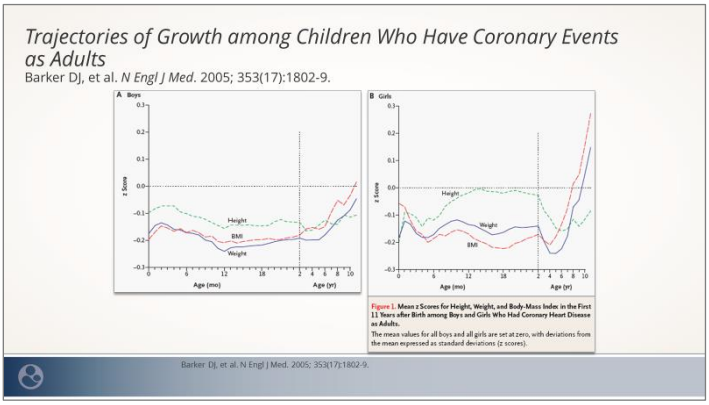
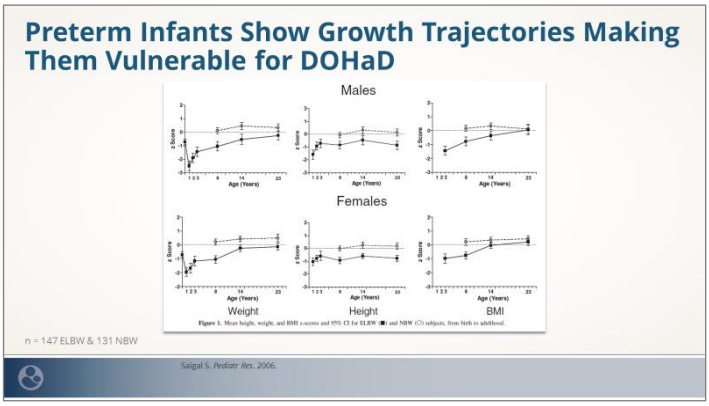
Why is the quality of growth important? You see here in this data [Slide 5] from David Barker, MD, PhD, FRS, that shows trajectories of growth amongst children with coronary events as adults, and it's for girls and for boys.[3] What you see is that these boys start a little lower, below average and then the height stays low, but the body weight increases during the prepubertal period, increasing therefore the BMI. These growth patterns predispose for a higher risk for coronary events as adults. That's the same for boys and for girls, as well.



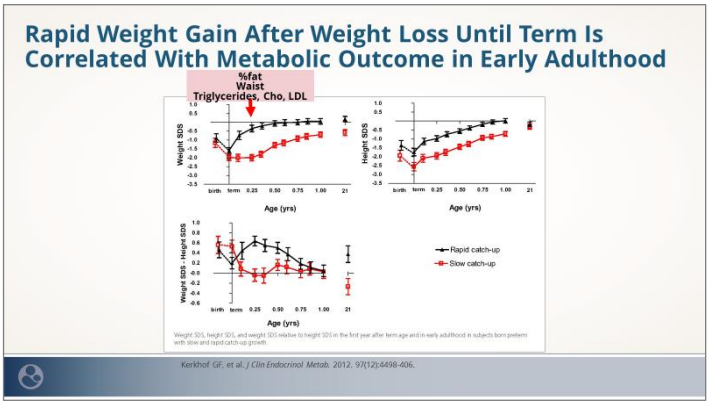
Slide 5 – Trajectories of Growth Among Children Who Have Coronary Events

Preterm infants show growth trajectories that look pretty similar. These are data from Saroj Saigal's, study [Slide 6].[4] She does a follow-up of ex-preemie babies, of ex-preemie group, and here are data up to 23 years. (There are no data available up to 35 years.) You see that the growth trajectories look similar: they are low, and then before puberty begins, the BMI increases. This makes kids vulnerable for DOHaD (Developmental Origins of Health and Disease) diseases.



Slide 6 – Preterm Infants Show Growth Trajectories Making Them Vulnerable for DOHaD

Early growth patterns with later metabolic outcome is also shown in this study of Gerthe Kerkhof, PhD, that relates different dynamics of growth to percentage of body fat, waist [circumference], triglycerides, cholesterol and LDL.[5] There are clear differences according to growth patterns that have been achieved. These are most babies that were "starved" after birth first, and then started to grow, with some catch-up growth.



Slide 7 – Rapid Weight Gain After Weight Loss Until Term Is Correlated With Metabolic Outcome in Early Adulthood

Postnatal Growth Retardation

This leads us to the problem of postnatal growth retardation. This is a study from Richard Ehrenkranz, MD, who compiled data about how babies grow.[6] You see it here, the 10th and the 50th percentile, those are the straight lines, and the dotted lines show typical growth trajectories of

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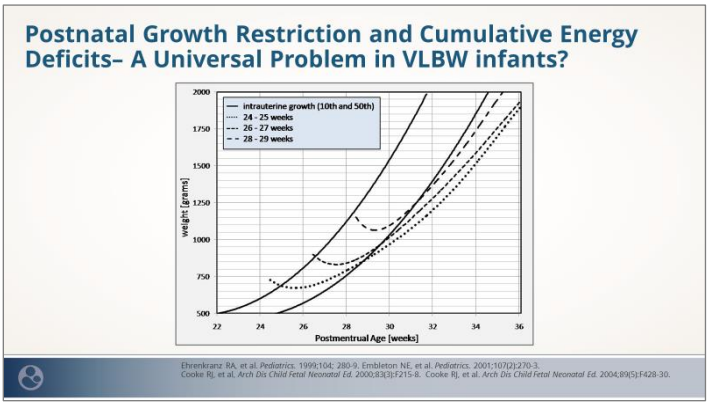
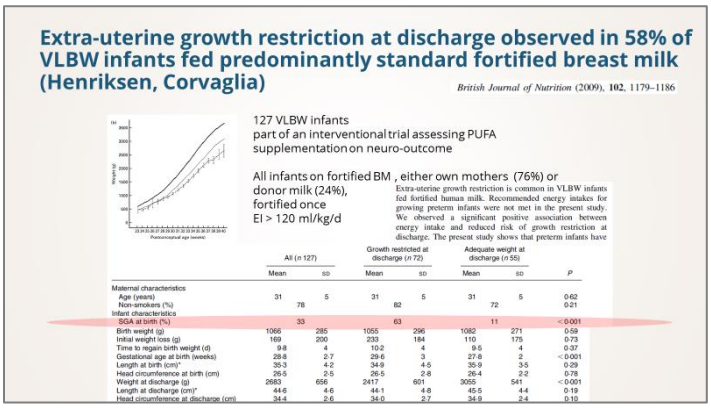
groups of babies who are born very preterm.



Slide 8 – Postnatal Growth Restriction and Cumulative Energy Deficits– A Universal Problem in VLBW infants?

This pattern definitely deviates from trajectories we would see in utero and is not compatible with what the American Academy of Pediatrics requests.

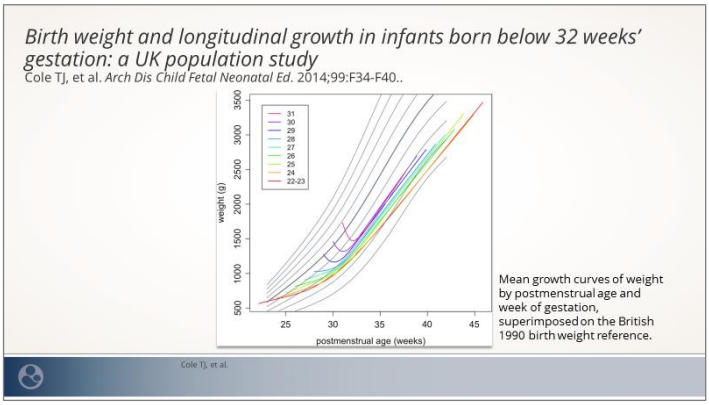
This problem of accelerated uterine growth restriction is also nicely illustrated in this study on 127 VLBW infants [Slide 9],[7] which were part of an interventional trial assessing polyunsaturated fatty acids. You see that the number of babies who were SGA [small for gestational age] at discharge is much, much higher compared to the entry point.



Slide 9 – Extra-uterine Growth Restriction at Discharge Observed in 58% of VLBW Infants Fed Predominantly Standard Fortified Breast Milk

There are very recent data from the Vermont Oxford Neonatal Network [Slide 9] that also show that the babies for the network, about 15%,[7] were SGA at admission, and about 45% SGA at discharge, showing that this is still a relevant problem.

These are very new data, also from the UK [Slide 10], showing growth trajectories of different babies, different gestational ages.[8] You see that they also deviate from their intrauterine trajectory, and it's not also the distance, but it's also the slope.



Slide 10 – Birth Weight and Longitudinal Growth in Infants Born Below 32 Weeks' Gestation: a UK Population Study

[You see] the significant variation of growth rates and nutritional strategies among NICUs, and it's a kind of an operator-dependent performance. You see in this study where 13 US [NICU] units have been compared.[9] So, its 15 US [NICU] units have been compared according to the growth rate that they achieve in the babies—this is from admission until discharge. You see there's a clear difference in the amount of growth that has been achieved. There are good performers and not so good performers.

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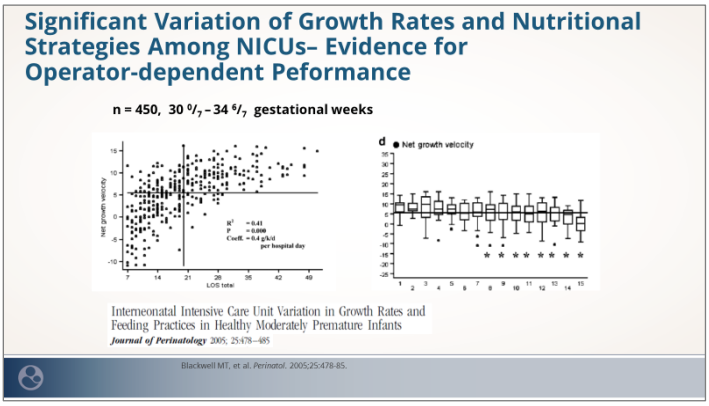
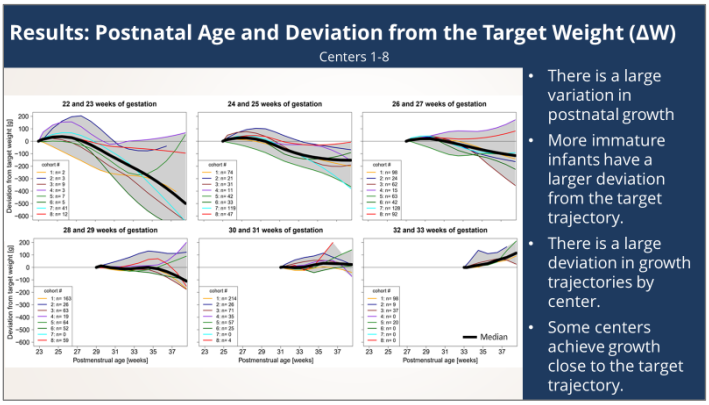


Slide 11 – Significant Variation of Growth Rates and Nutritional Strategies Among NICUs– Evidence for

The whole business has some operator dependence.

Here you see data from a comparative study we [McMaster University] did recently [Slide 12], by compiling data of a few big [NICU] units.[10] I will show you later which units [NICU] these are. You see here the growth trajectories of the different gestational ages; there's a huge variation. Each line gives a certain center, and the more immature infants have a larger deviation from the target trajectory. There is a large deviation in growth trajectories by center.

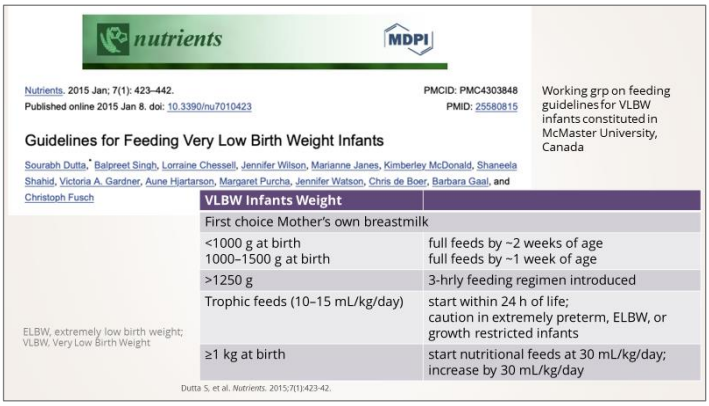


Slide 12 – Results: Postnatal Age and Deviation from the Target Weight (ΔW)

We presented that last year at the PAS [Pediatric Academic Societies] meeting. There are very renowned units [NICU] in there, like Karolinska University, Stockholm, and also [Brigham and Women's Hospital] Boston and other units [NICU] with great names, and we still see this difference in practice.

Factors that can aggravate nutrition intake are delayed nutritional support, slow postnatal enteral feeding advancement, prolonged use of parenteral nutrition, repeated bouts of feeding intolerance, providing nutrition that does not offer optimal composition, and nutrients needed for high growth rates in preterm infants—we'll come to that later—and lack of proper postnatal reference trajectories.[11]

Let's first talk about the *how*, the *know-how*. Guidelines for feeding very low-birth-weight infants are very, very helpful; this has been shown multiple times. I can only encourage people to use and implement guidelines like these or others in the [NICU] unit.[12]



Slide 13 – Guidelines for Feeding Very Low-Birth-Weight Infants

A few years ago, in the University of Greifswald, we did a trial and tried to optimize postnatal growth by starting enteral intake earlier, incrementing it faster, and also allow maximum intake up to 200 ml/kg/d, and starting parenteral nutrition earlier. There was a historical control [group]. The intervention study was done later than the comparison study.

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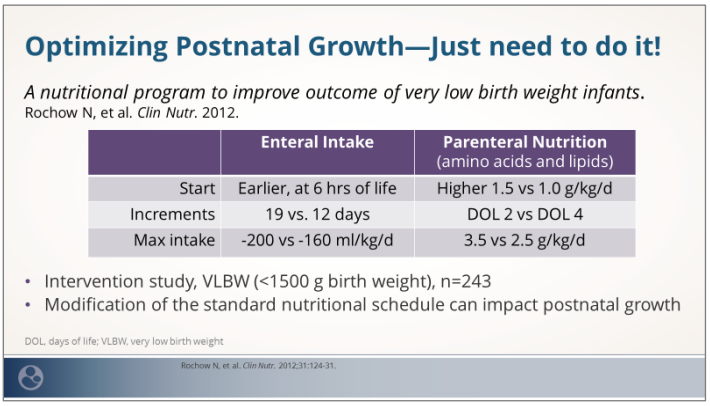
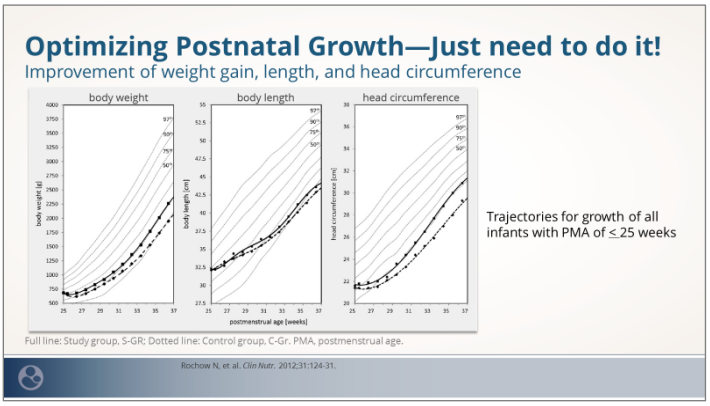


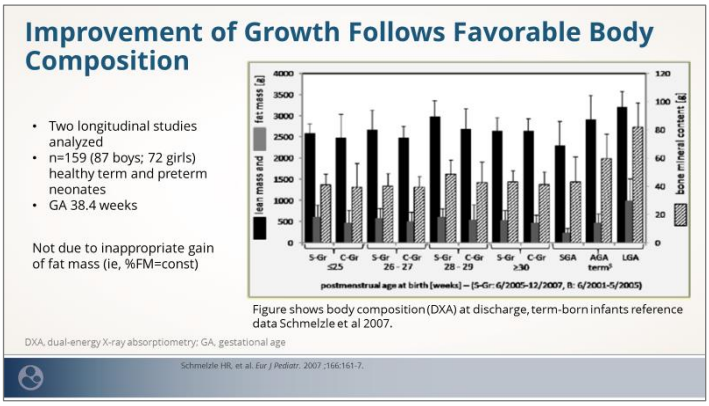
Slide 14 – Optimizing Postnatal Growth

These are the differences that we achieved [Slide 15].[13] For body weight there's a group for babies below 25 weeks. We saw a clear increase in the trajectories, and they were now more parallel to the fetal growth rates. That was also true for the head circumference. That was true because every baby got ultrasounds, and at the end, also an MRI.



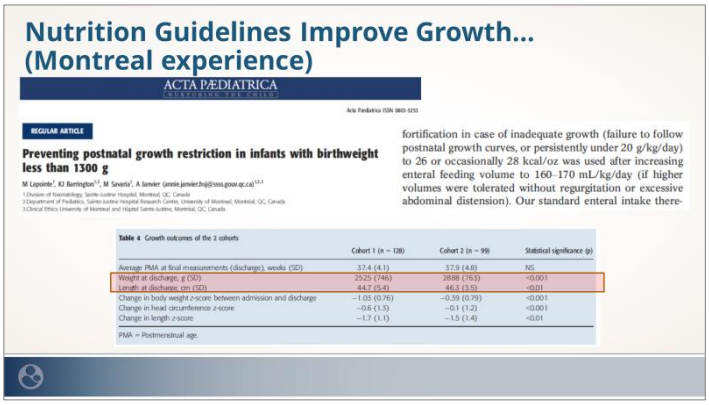
Slide 15 – Optimizing Postnatal Growth (cont)

We did not increase body fat, in terms of body composition. The babies at discharge had the same amount of body fat compared to AGA [appropriate for gestational age] babies at term, saying how we provided the food led to a good body composition, a standard body composition.



Slide 16 – Improvement of Growth Follows Favorable Body Composition

There are more data now and more studies coming out. This was a recent study from Montreal [Slide 17], where they also increased the nutritional intake—allowed up to 170 mL/kg/day.[14] I experienced the difference in volumes that are allowed in Europe, where we easily go up to 200 mL/kg/day. Whereas in North America, we frequently restrict to 150–160 mL/kg/day because of the fear of BPD [bronchopulmonary dysplasia], but it doesn't seem to be correlated.



Slide 17 – Nutrition Guidelines Improve Growth

There are more studies coming out, as a growing body of evidence about prevention of postnatal growth restriction. Most are single-center experiences.[15]

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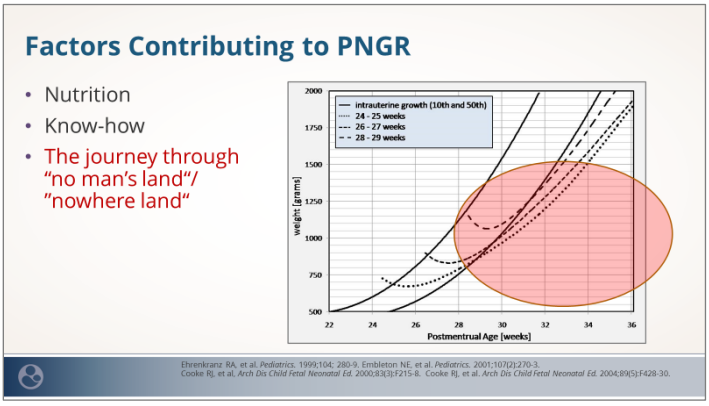
Physiology of Postnatal Adaptation and Growth

This is about the *how*, the *what to do*. I'm now talking about the development of adequate postnatal trajectories to give guidance to clinicians for how to [manage] food. Precision nutrition starts, therefore, with a growth goal that can be assessed, and we need tools available to monitor accuracy of growth trajectories.

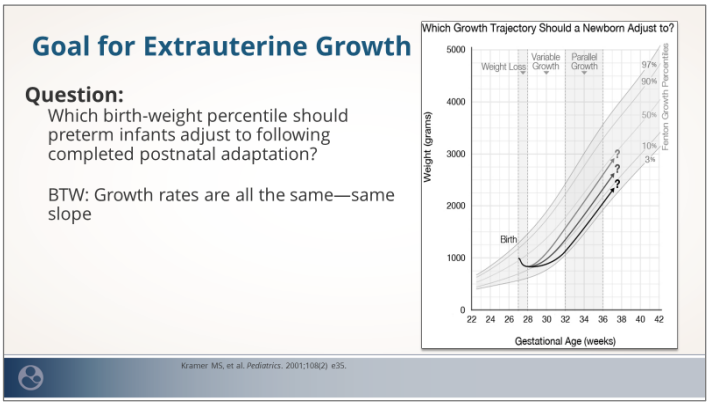
If we go back to this slide—we have seen it before from Richard Ehrenkranz, MD[6]—then I would like to point out we have this problem of the journey through "no man's land" or "nowhere land."



Slide 18 – Factors Contributing to PNGR

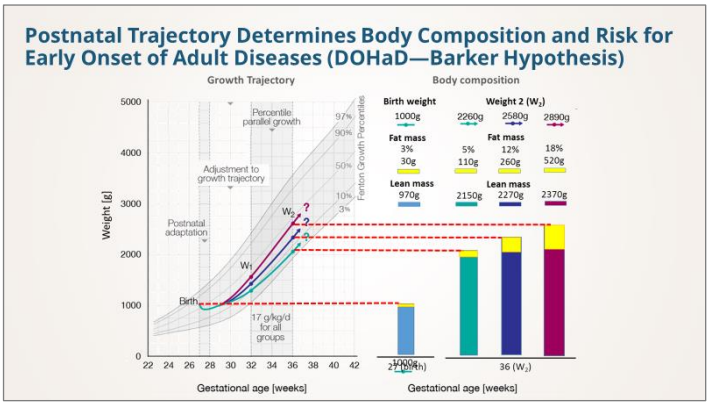
We don't have clear guidance where a baby should grow after birth. Some are happy if we seek growth trajectories like this; some are happy if the growth trajectories are a little bit closer to parallel. But nobody exactly knows how a baby should grow postnatally. We've tried to look into this problem during the last years and have published a few papers on that.

Basically, you can imagine that all these 3 trajectories have more or less the same weight gain, because the slope is the same, and the weight is also more or less the same. Overall, the growth rates are the same for all 3 trajectories shown here [Slide 19].[16] The lower one, indeed paradoxically, shows a little higher weight gain, because the denominator (the weight) is smaller, but the slopes are the same.



Slide 19 – Goal for Extrauterine Growth

Does it matter? *It matters.* If we break it down here to body composition [Slide 20], the yellow one is the fat, and the other colors are the lean body mass. You see that the lean body mass increases a little, but what mostly increases here is fat mass. I gave you some true numbers of babies whose body composition have been measured at different percentiles.



Slide 20 – Postnatal Trajectory Determines Body Composition and Risk for Early Onset of Adult Diseases

As we've seen before, the amount of body fat that is being accreted should not be too low, but should also not be too high to get an optimum risk for DOHaD [Developmental Origins of Health and Disease]. That's why these growth trajectories matter where they are being positioned in these reference charts.

How do we monitor weight gain? We have these postnatal curves for where we combine intrauterine

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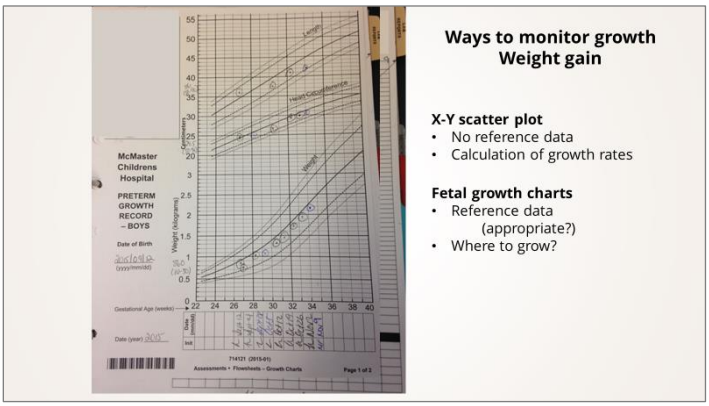
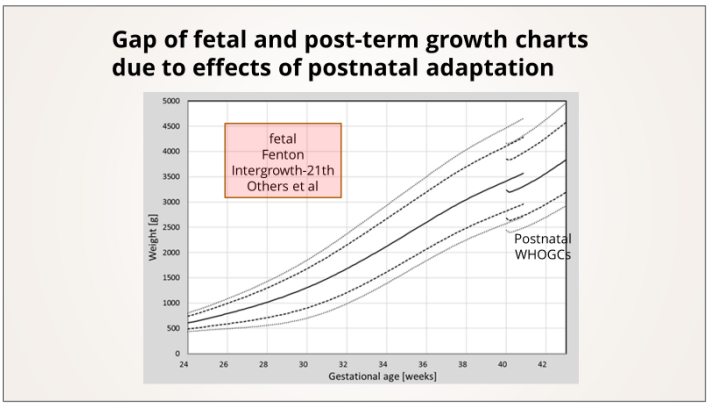
and postnatal growth—great work has been done by Tanis Fenton, PhD, RD, and I think many NICUs use it, and they plot weight like this [Slide 21].[17]



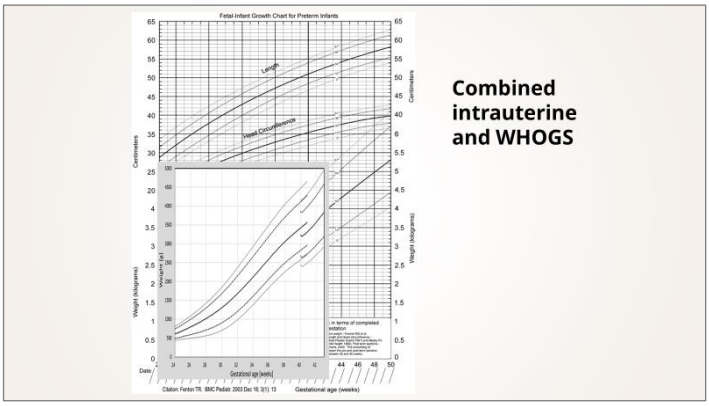
Slide 21 – Ways to Monitor Growth (Weight Gain)

If we look into how these have been created, then they are compositions of 2 data sources: one is the fetal data, like the one Fenton published, or INTERGROWTH-21st data or others; there are few additional resources available, *plus* the postnatal growth data from the World Health Organization growth charts of term babies.[18] You see that there is an offset between these 2 [Slide 22], which mainly has to do with postnatal adaptation.



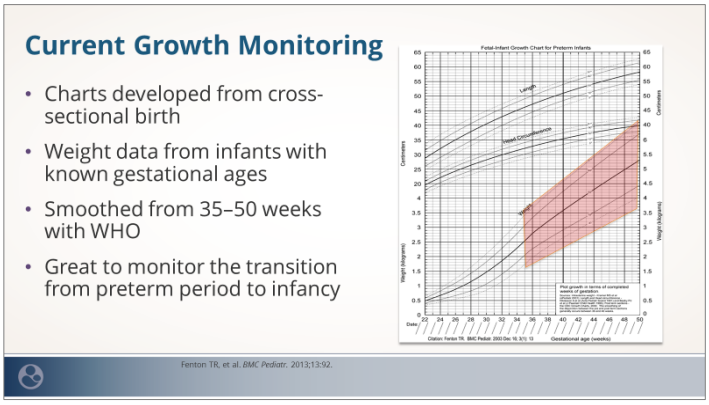
Slide 22 – Gap of Fetal and Post-term Growth Charts Due to Effects of Postnatal Adaptation

The Fenton curves have been linearly extrapolated from around 33, 34 weeks up to 50 weeks, and combined both with a straight line like this one.



Slide 23 – Combined Intrauterine and WHOGS

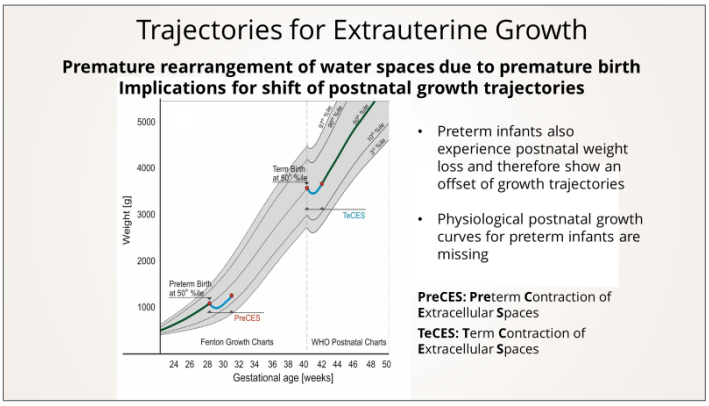
This is the data we work with, and it is a great way to monitor transition from preterm period to infancy, but it doesn't give guidance on the individual baby—how the baby should grow.



Slide 24 – Current Growth Monitoring

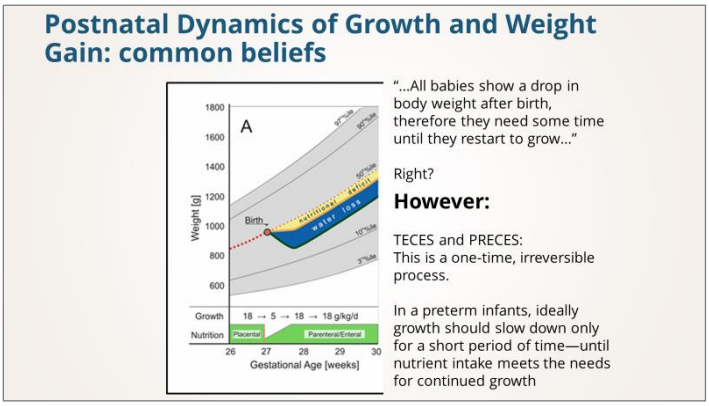
If we look at what term babies experience after birth, and why intrauterine and extrauterine charts have a little offset, then we can see that all babies lose weight after birth. This is mainly due to a loss of body water and not growing as much as they do in utero for a short little period.

State of the Art: Precision Nutrition in Preterm Infants



Slide 25 – Trajectories for Extrauterine Growth

Preterm babies do the same. They have this adaptation a bit earlier, but then don't do the second drop at term, but [rather] grow continuously.

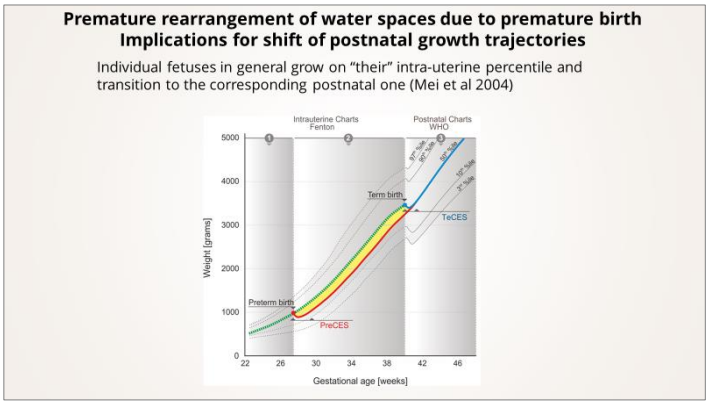


Slide 26 – Postnatal Dynamics of Growth and Weight Gain

A term baby loses weight at term and shifts the percentile; whereas the preterm baby shifts the percentile a little earlier, and then should regain the percentile on which it would have grown until term, back again.

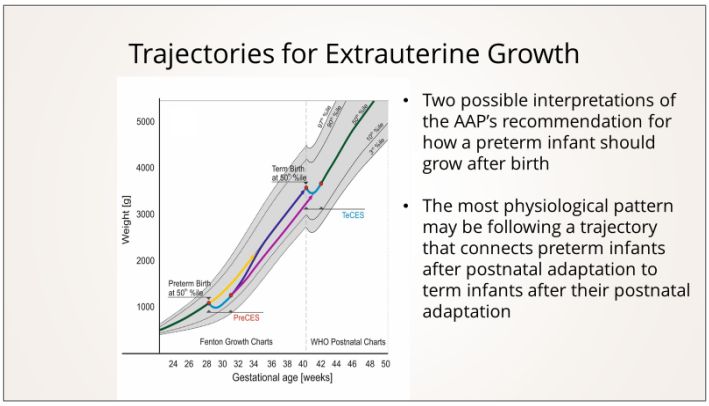
If we look into the nature of this loss of weight gain, then it is a combination of 2 things: it is not enough nutritional support during the first few days—because babies are starving a little bit—but the major part is due to a loss of body water, and it's mainly contraction of extracellular fluid by about one-third. This is an irreversible process that has never been compensated and happens only once in a lifetime—it's in postnatal adaptation of the body from intrauterine to postnatal environment.

Again, a baby stays either in utero, and does this adaptation at term, or it does this adaptation preterm, but not again at term. [It's basically like in New York City, you go first straight and then to the right to come to the Empire State Building, or you go first to the right and then go straight forward and meet it there.]



Slide 27 – Premature Rearrangement of Water Spaces Due to Premature Birth

Now the question is: can we create trajectories that are helpful for neonatologist? For this, we need to find the point for the preterm baby that you see here: PreCES, which is a Preterm Extracellular Contraction. Can we find this point at 7–21 days after birth, as a kind of postnatal adaptation of the babies?



Slide 28 – Trajectories for Extrauterine Growth

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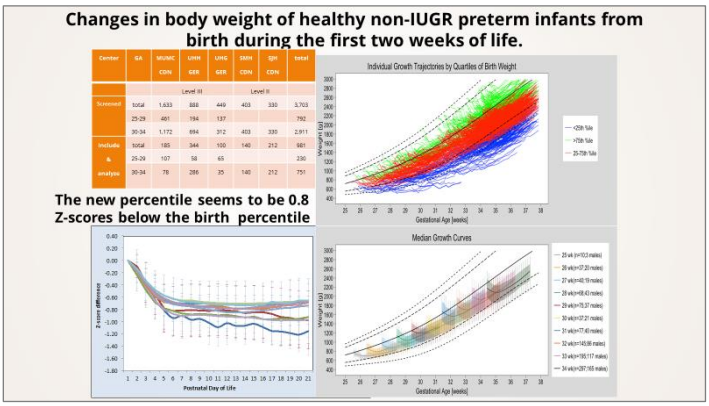
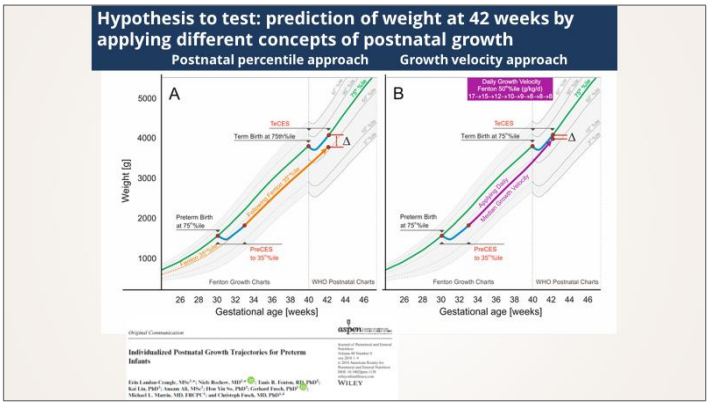
We did a study where we looked into healthy preterm babies out of a group of 3700 preterm infants in 5 clinics (3 in Canada, 2 in Germany), and then took only the babies with a most undisturbed transition with predefined criteria.



Slide 29 – Changes in Body Weight of Healthy Non-IUGR Preterm Infants From Birth During the First Two Weeks of Life

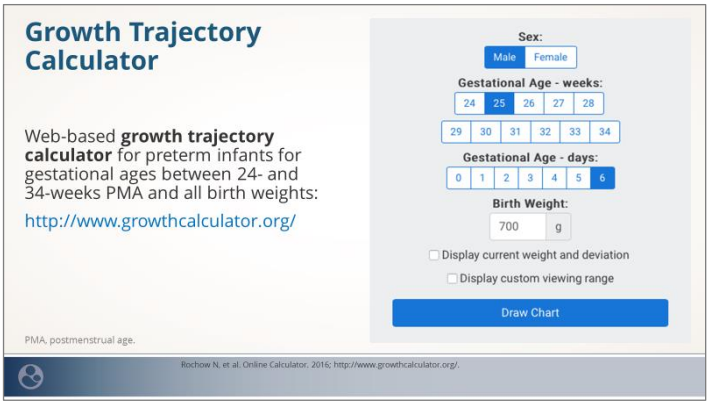
We ended up with 1000 babies, from 34 down to 25 weeks [gestational age]. The funny thing is that they adapted all the same way to about 0.7 Z-scores, which they reached in 5–7 days. After that, they stayed on Z-score. It looked like it created new postnatal percentiles, so we measured that and constructed prediction equations; [we] could find for each baby, with a pretty precise estimate, this weight at 7 and 21 days. The interesting thing is there were no differences between NICUs, despite moderate differences in fluid and nutritional protocols, which means that healthy preterm babies might be able to handle the differences between 10, 20, or 25 mL/kg/d. [It] doesn't matter so much.

Now, from 21 days, which is the end of the blue line down [Slide 30], we need to find a trajectory that connects us to 42 or 44 weeks of gestational age, to get the point that we called TeCES [Term Contraction of Extracellular Spaces]. We found a way to calculate this trajectory and validated it.



Slide 30 – Hypothesis to Test: Prediction of Weight at 42 Weeks by Applying Different Concepts of Postnatal Growth

The important thing is the **growth trajectory calculator** [Slide 31], which is available online [http://www.growthcalculator.org/], creates these curves according to gestational age, according to the gender, and also according to the percentile of body weight at which the baby was born [Slide 32]. These trajectories can now give clinicians guidance, how to monitor growth and how to adjust nutrition, because you see more easily when babies are falling off the expected trajectory.



Slide 31 – Growth Trajectory Calculator

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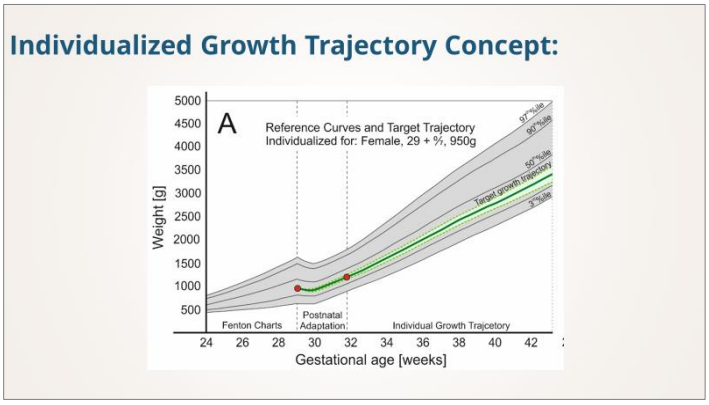
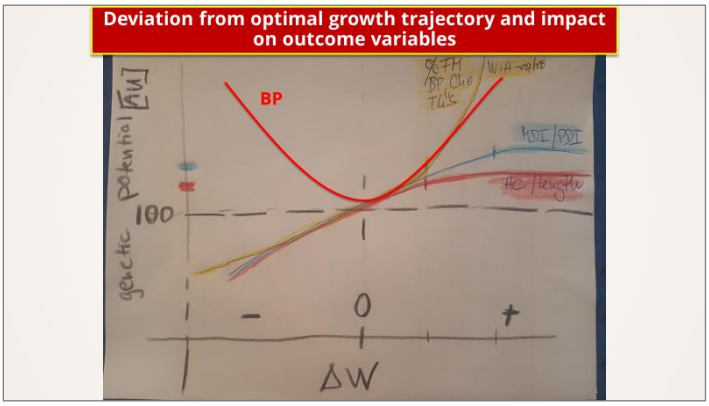


Slide 32 – Individualized Growth Trajectory Concept

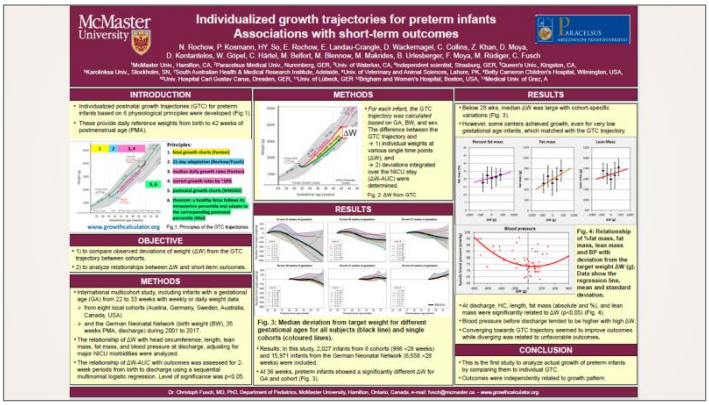
We validated these trajectories, and the important thing is the delta weight (ΔW) from the baby at discharge—or at around term—compared to the weight that it would have had if it stayed on its intrauterine trajectory.



Slide 33 – Deviation from Optimal Growth Trajectory and Impact on Outcome Variables

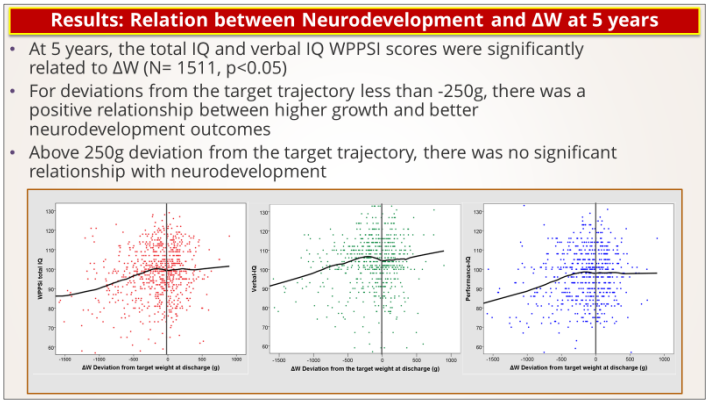
If the theory is right, then this **ΔW—the difference from the true weight at discharge compared to the target weight**—should be related to [the] outcome. That should be different for blood pressure; it should be different for fat mass, and should be different for head circumference, as well as neurodevelopmental [outcome]. I've shown this in the different colored graphs [Slide 33].

We started work together with 8 international NICUs and got neonatal outcome data from preterm babies, and could correlate them to the discharge weight difference. Here are the results [Slide 33].[10]



Slide 34 – Individualized Growth Trajectories for Preterm Infants

In the lower right, you see the red graph, which is about blood pressure, and you see it indeed shows this U-shaped curve. For neurodevelopmental outcome at 18–24 months, and also at about 5 years, you also see an increase [IQ] until the ΔW of 8, and then it becomes flat. The characteristics behave as we expected. So, it's a strong indicator that these individualized trajectories might work.



Slide 35 – Results: Relation Between Neurodevelopment and ΔW at 5 years

Currently, California is doing work with these curves, and Portugal is also trying to use these curves for their individual guidance.

Nutrition Physiology for Growth

Now, *how do we achieve growth once we have better identified how babies should grow?* We need to go a

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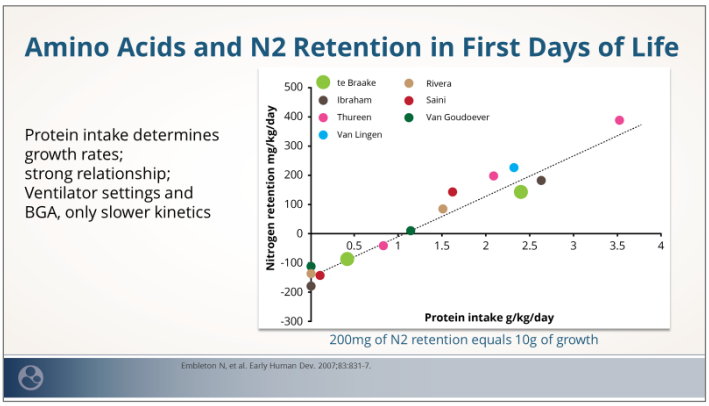
little bit into the nutrition physiology. On this graph [Slide 36],[19] you see the relationship between protein intake on the x-axis in g/kg/d vs nitrogen retention [y-axis], which is a parameter for building up lean mass. You see the calculation 200 mg/kg/d of nitrogen retention equals 10 g of growth.

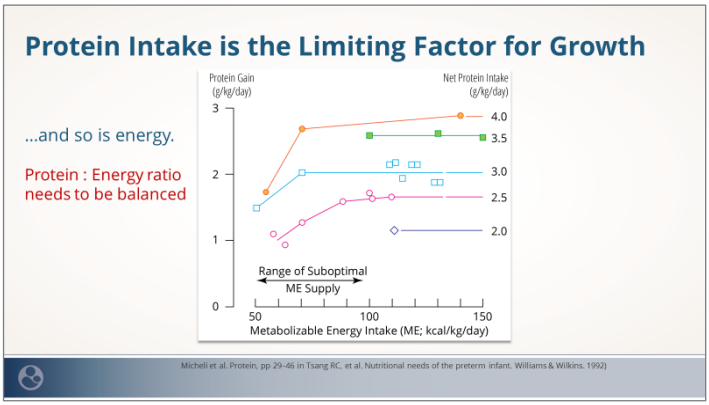


Slide 36 – Amino Acids and N2 Retention in First Days of Life

So, you need to have an intake of 1 g/kg/d of protein not to grow. If your intake is below this, then you lose lean mass. If you increase protein intake beyond 1 g/kg/d up to 3.4–4 g/kg/d, then you achieve an increase in lean mass. This goes up to 20 g/kg/d [growth] at around 3.5–4 g/kg/d protein intake.

This relationship is very, very strong; it is very linear. You can, therefore, influence growth by adding enough protein.

However, we also need to look into energy. What you see here on the x-axis is the metabolizable energy that is being filled into the baby [Slide 37], and on the right side, you see the protein intake ranging from 2.0–4.0 g/kg/d.[20] You see the protein gain on the left side and that there is a kind of saturation kinetics.



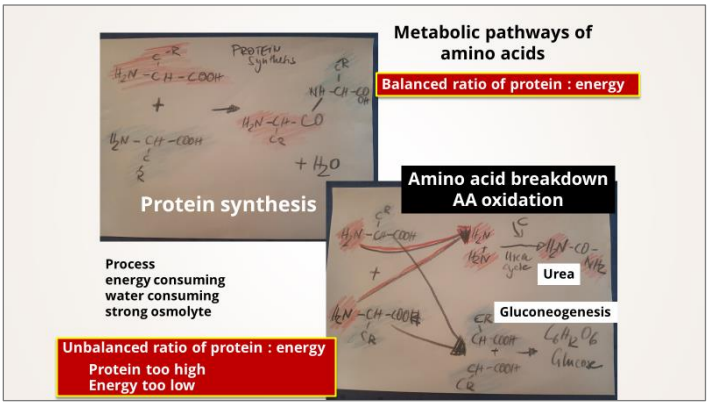
Slide 37 – Protein Intake Is the Limiting Factor for Growth

Let's look at the baby who receives 2.0 g/kg/d as protein (on the right side), and you see that you achieve an optimal intake if you give 100 kcal/kg/d. If you give more energy, there is no better buildup of protein mass because all the building blocks are being used already, and more energy would lead to more fat deposition.

If you give less energy, then, although you give the same amount of protein, the protein gain would be decreasing, because there's not enough energy provided. If you want to increase growth at a certain kind of energy, then you have to give more protein and also more energy. So, **energy and protein need to be in a balanced ratio**. There's no need to look only at protein if you do not fulfill the energy needs. There's no need to give too much energy if you don't have enough protein in there. Keep that in mind later when we look at the composition of breast milk.

What happens in this unfavorable situation is that the 2 amino acids you see on the left side [Slide 38, top], the red and blue, are being put together to form proteins, if there is enough energy available. If not, then amino acid breakdown occurs, and the carbon skeleton is being stripped of the nitrogen skeleton, and the nitrogen is being used to form urea to get rid of the nitrogen. That is a very energy- and water-consuming process, [which is] an

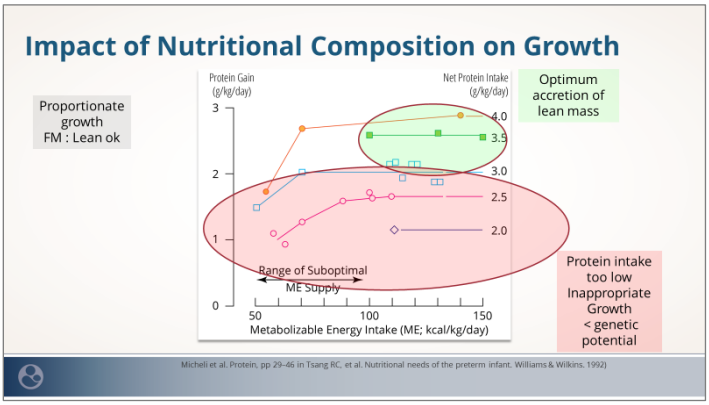
unfavorable metabolic pathway for amino acids. It's called amino acid oxidation.



Slide 38 – Metabolic Pathways of Amino Acids

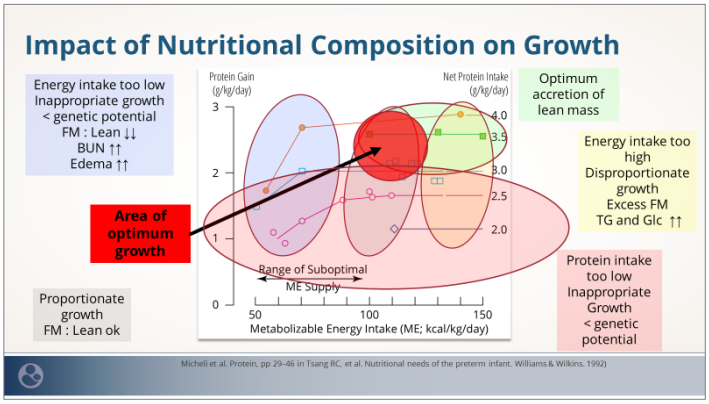
This is what we would like to avoid, because we would like to see the proteins being synthesized and not used for energy production.

If we go back to this slide [Slide 39], where we have energy and protein intake,[20] then you would achieve optimal accretion of lean mass in this green range. In this pink range, the protein increase would be too low because you don't give enough protein and your growth stays below the genetic potential.

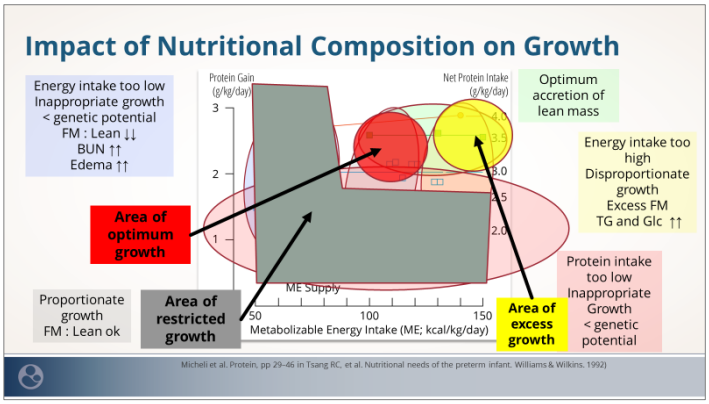


Slide 39 – Impact of Nutritional Composition on Growth (expanded)

At the end, you can look for different combinations, and you get different growth or non-growth areas. The area of optimum growth would be here [Slide 40, red oval]. The yellow would be the area of excess growth, where we might get too much deposit of fat mass [Slide 41]. The gray area is where babies would not grow in a good way, nor in a good body composition.



Slide 40 – Impact of Nutritional Composition on Growth (expanded)

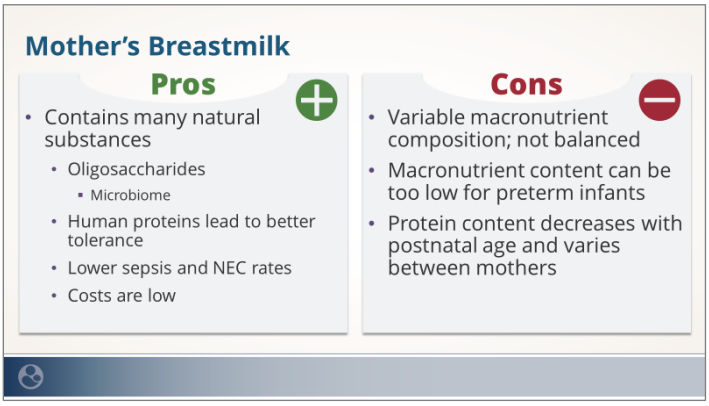


Slide 41 – Impact of Nutritional Composition on Growth (expanded)

How Nutritional Needs Vary Among Preterm and Term Infants

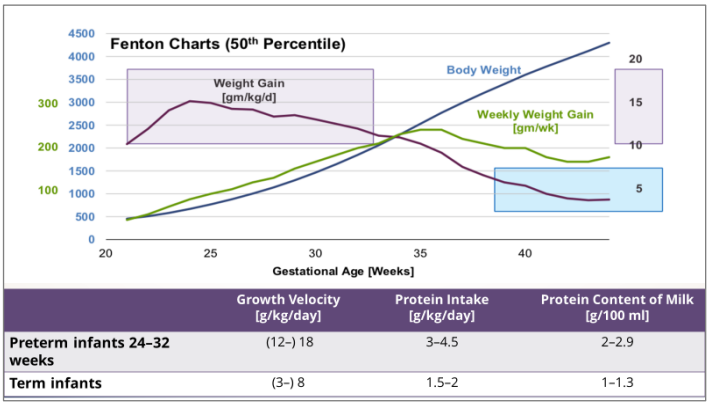
We would like to feed babies with mother's breast milk. For the preterm babies, because we know that the composition is favorable, it prevents necrotizing enterocolitis (NEC), and the tolerance is better. However, the macronutrient content of breast milk is very variable—it is not balanced. (I will show data on that a little later.) The macronutrient content will be too low for preterm infants. Plus, the protein content of breast milk decreases with postnatal age and varies between mothers, which is fine for term babies because growth rates are much lower compared to preterm babies, but term babies are also self-regulated. If they get breast milk with a

certain composition, they sense it, and they drink more or less. If they get breast milk with a different composition, then they can adjust it. That is similar to when we eat fondue bourguignonne, which is made from meat, or Swiss fondue with cheese; our eating behavior is different. That's the same for term babies.



Slide 42 – Mother's Breastmilk Pros and Cons

Let's have a look into intrauterine growth trajectory percentiles and growth rates. You see that the weight gain in g/kg/d is low at term [Slide 43]. It's around 5–8 g/kg/d, which when you take the data I showed you before into account, protein intake would need to be 1.5–2 g/kg/d for a baby to grow appropriately. At an intake of 150 mL/kg/d, the protein content of that milk would need to be 1–1.3 g/dL. This is exactly what breast milk usually is because it has been created from Mother Nature for optimal nutrition of term babies.

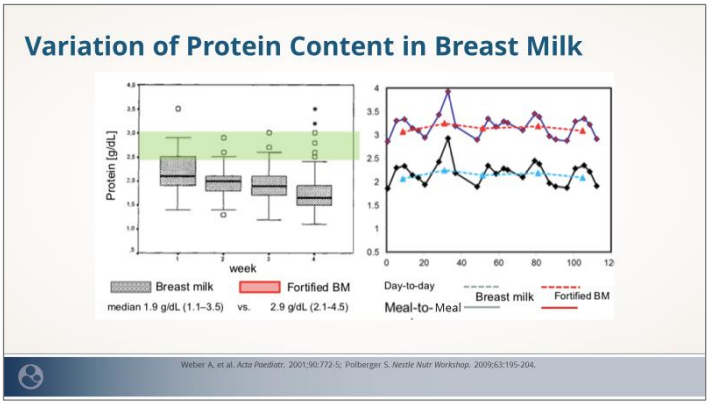


	Growth Velocity [g/kg/day]	Protein Intake [g/kg/day]	Protein Content of Milk [g/100 ml]
Preterm infants 24–32 weeks	(12–) 18	3–4.5	2–2.9
Term infants	(3–) 8	1.5–2	1–1.3

Slide 43 – Intrauterine Growth Trajectory Percentiles and Growth Rates

Preterm babies' growth rates are much higher; they are around 12–18 g/kg/d, sometimes up to 20–22 g/kg/d. With this, they would need the protein intake of 3–4.5 g/kg/d, and the protein content of milk would need to be between 2 and 3 g/dL, which is not available in breast milk. The neonatal community has developed routine fortification with human milk fortifiers as an approach towards that.

You see in this slide on the left graph [Slide 44], the protein content of 10 mothers over the period of 4 weeks (these are old data).[21] It shows that there is a decrease during the first 3–4 weeks, but there's also a large inter-individual variation of protein content.



Slide 44 – Variation of Protein Content in Breast Milk

The green area is the area of ESPGHAN [European Society for Pediatric Gastroenterology, Hepatology and Nutrition] recommendations, what the fluid babies are drinking should contain as protein.

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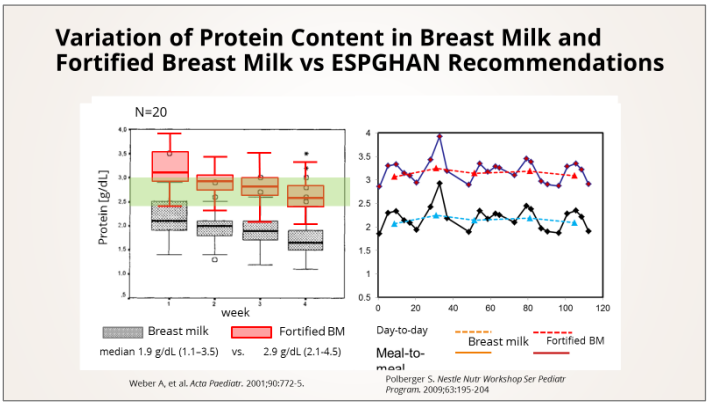
There's still insufficient growth of preterm babies on fortified breast milk. It's about 60% of the VLBW babies who do not grow perfectly under standard fortified breast milk.

Why is that the case? Because all [of this] is based on the major assumption of an average composition of breast milk, which is not correct for all preterm infants, and can lead to significant over and under nutrition. This effect is also frequently not taken into account in the design and interpretation of clinical studies, as well as conclusions drawn from such results.

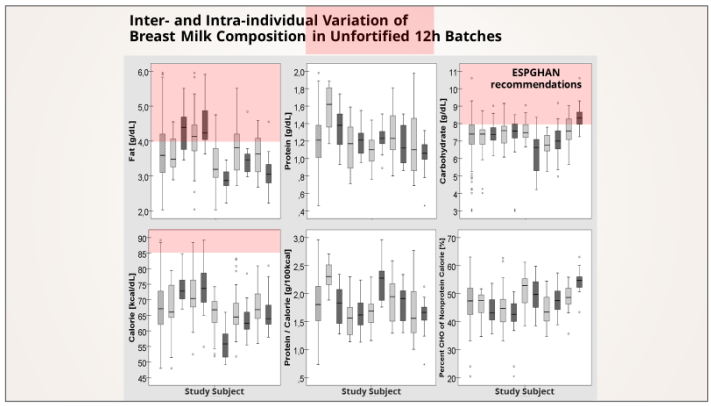
This is what happens [Slide 45]. You see the same graph, and now we have added the fortifier. You see during the first 1–3 weeks for most of the mothers, the milk contains enough protein, but already in week 4, you see some milk are falling below, outside of the shaded area, and the protein concentration will decline further.



Slide 45 – Variation of Protein Content in Breast Milk and Fortified Breast Milk vs ESPGHAN Recommendations

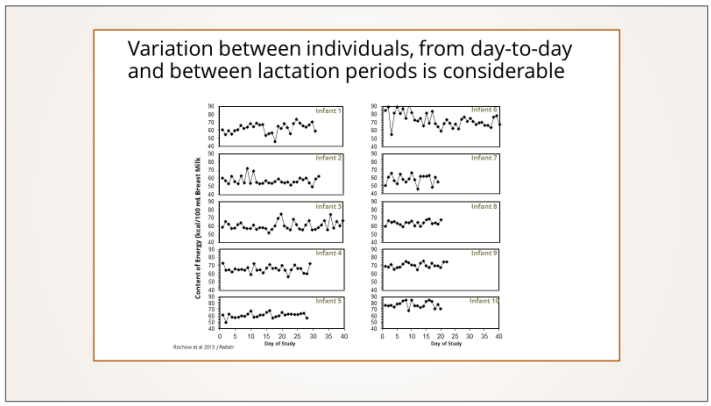
You see after 4–5 weeks, there are already 30–40% of the babies who would not receive enough protein with standard fortified breast milk. A 24-weeker at 4–6 weeks (28–30 weeks) still has a long way to go until term, until we can feed him with normal breast milk, provided we have achieved proper growth rates at that time.

These are data of the true variation of breast milk from our study [Slide 46].[22] These are 10 moms, and this is a variation in fat, in protein, and in carbohydrates—lower down, for calories, for protein-to-energy and for carbohydrate-to-fat ratios. You see there is a huge variation between mothers but also within mothers. So, the **breast milk is a highly variable diet for a preterm baby**.



Slide 46 – Inter- and Intra-individual Variation of

Here you see longitudinal assessment of energy content in these 10 mothers, and you see the intra-individual variation [Slide 47]. Some are at 55 kcal/dL others at 70 kcal/dL. We are calculating with average values, and you see that is not always true.



Slide 47 – Variation Between Individuals, from Day-to-day and Between Lactation Periods is Considerable

What opened up my eyes was this plot [Slide 48],[23] where we took 850 milk samples that we had data on and did an X-Y plot for the different macronutrients: lactose vs protein, fat vs protein, and also fat vs lactose. What you see is the data are all over the place. There is not thick, rich milk, rich in

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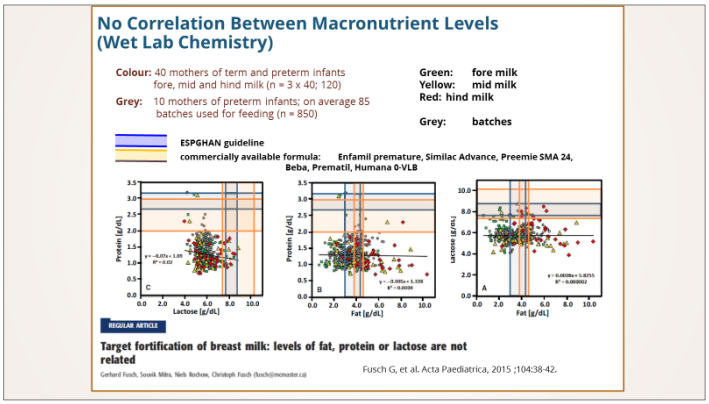
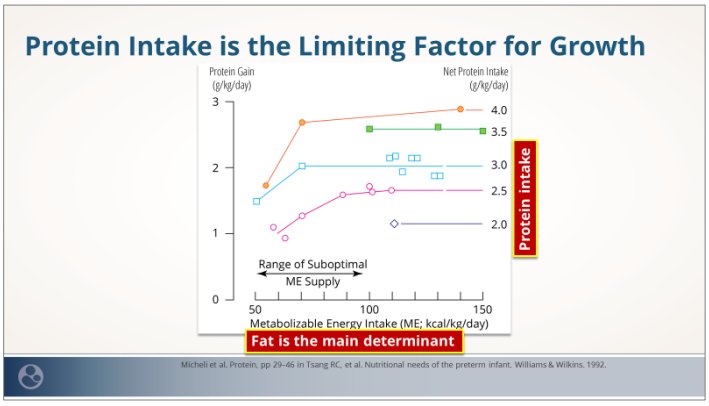
all macronutrients, and a kind of diluted milk. That is what I thought before. No, each milk is composed in a different way. You can receive and you can feed milk to babies who are low in protein and are very high in energy, and milk that is very high in protein and very low in energy. These babies cannot grow, even if you give them more, because you violate the assumptions that are needed to give the proper protein-to-energy content.



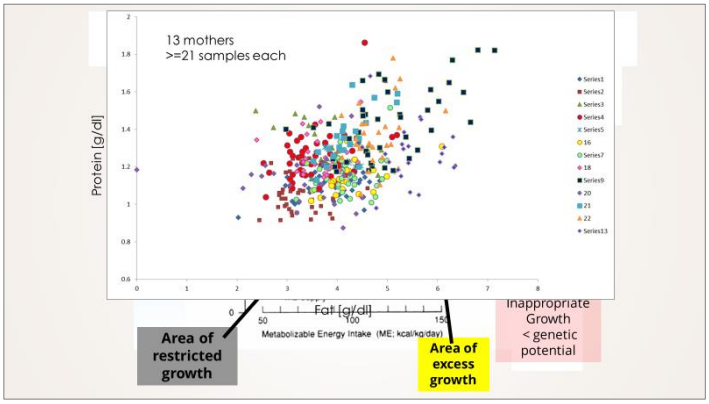
Slide 48 – No Correlation Between Macronutrient Levels

Let's go back to this slide [Slide 49]. On the x-axis you see the metabolizable energy, for which fat is the main determinant, and on the y-axis you see the protein intake, for which protein intake is obviously the main determinant.[20]

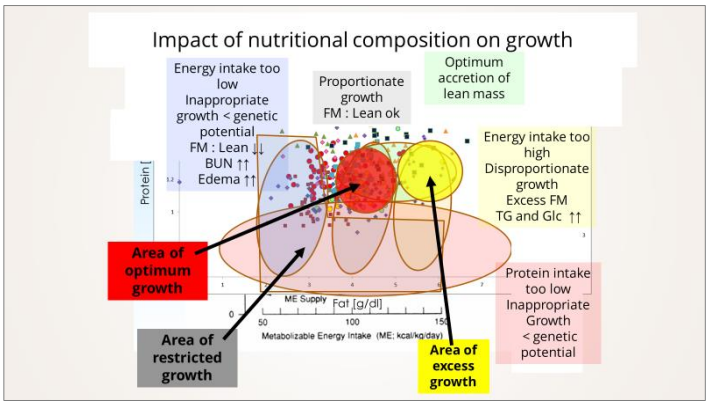


Slide 49 – Protein Intake Is the Limiting Factor for Growth (expanded)

If we now take this slide [Slide 50], where you see the plots of 13 mothers, they are color coded by mother. X-axis is fat, which is energy content; y-axis is protein. And you do an overlay [Slide 51], then you see there are mothers providing breast milk with a composition that would lead to an improper and unfavorable growth in certain preterm infants. That's exactly what we observed in clinical routine.



Slide 50 – Impact of Nutritional Composition on Growth (pt 1)



Slide 51 – Impact of Nutritional Composition on Growth (pt 2)

Preterm infants have no self-regulation. This is different from term infants. Just adding more of an unbalanced diet does not help fix the problem.

Principles of Adjusted Fortification "Precision Medicine"

What do we give babies, which leads to the point that we need to adjust fortification? This is about individualized fortification.

One of the ways to do it is adjustable fortification of breast milk. This is a study done by Ekhard Ziegler's group.[24] They had 6 fortification steps that you see on the left lower corner. They increased to the next

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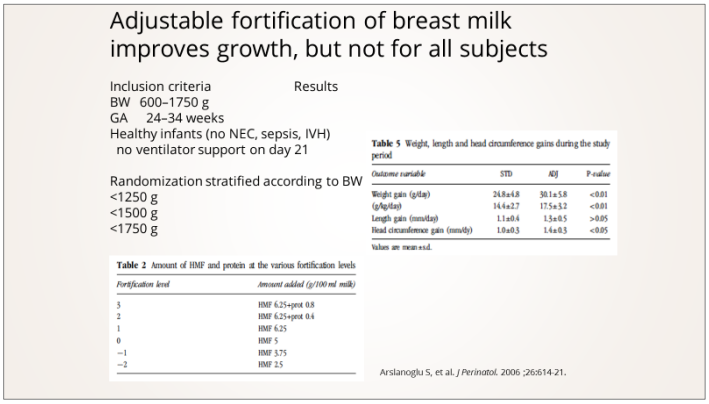
step when the BUN [blood urea nitrogen] concentration was low, and they decreased when the BUN level was above a certain limit.

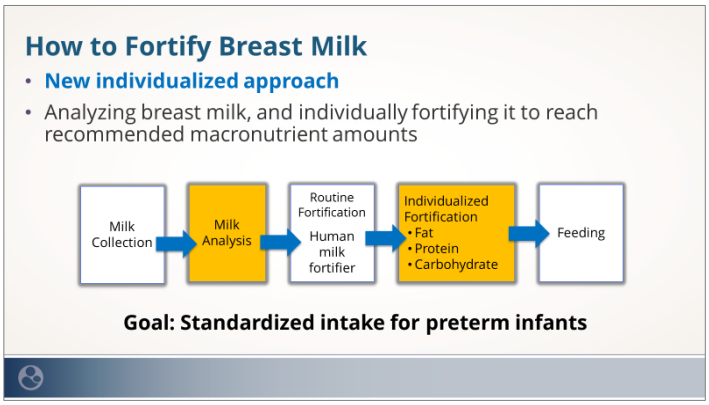


Slide 52 – Adjustable Fortification of Breast Milk Improves Growth, But Not for All Subjects

On the right side you see standard fortification (STD) and adjusted fortification (ADJ). You see that the adjusted fortification leads to better growth in terms of weight, in terms of head circumference, and length. However, what you also see is that there's still a significant variation of growth, as you see from 14 ± 2–3 g/kg/d, which means there are still babies who grow only with 11 and 10 g/kg/d, which might not be sufficient.

A problem with adjustable fortification is that you always have to wait for the BUN [determination], and also the cut-off levels for increasing or decreasing for the next fortification step, [which is] somewhat arbitrary. They might be right, but we don't know what the exact values are. But it is one way to achieve better growth in breastfed babies on standard fortification.

Our [methodology] was to do an individualized approach by measuring and finding what is missing, and then adding [fortification], which means we have to add milk analysis and then add the [fortification] components, which are the two additional [steps] [Slide 53, yellow boxes], that we have to implement in clinical routine.

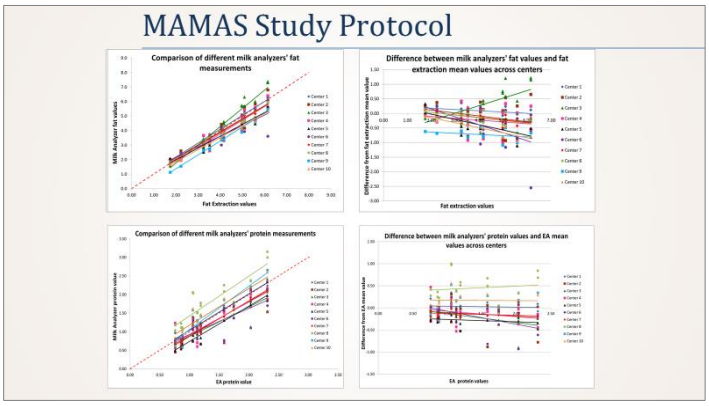


Slide 53 – How to Fortify Breast Milk

There are ways to measure the milk content at the bedside by using [point-of-care **milk analyzers**]. They were originally developed for use in the dairy industry, so they needed some work. We have worked for about 4 to 5 years to understand these devices better, and also to help improve the precision of these devices. The good thing is that at least one of them is now FDA approved for use [in the NICU]. Originally, there was a big deviation of the data, which has to do with cow's milk being different from human milk.

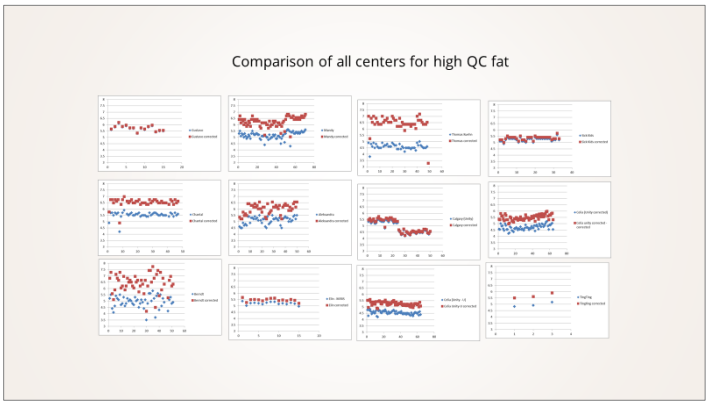
A study we did recently is that we sent out the same samples to [NICU] units in Europe, the US, and Canada, and did a kind of quality control study that has been published recently in *Clinical Nutrition* by Celia Kwan, one of our great students.[25] This is what came out of it [Slide 54]. You see on the x-axis, the true values; on the y-axis is always the measured values between the different NICUs, and you see that there is a large, large variation. You can imagine what would happen if target fortification studies were done with this kind of quality of measurement; we would get completely unreliable results.

State of the Art: Precision Nutrition in Preterm Infants

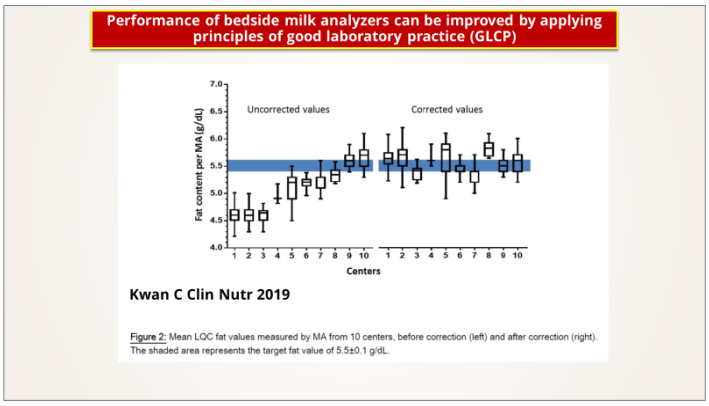


Slide 54 – MAMAS Study Protocol

That's why we did a quality improvement study on that education. Here you see the data from the different NICUs [Slide 55]. Obviously, there were some preanalytical errors. We could get that under control, and you see here [Slide 56], how, with education, the values were much better. We strongly encourage applying principles of good laboratory practice, similar to what we do with blood glucose measurements of blood gas analysis.



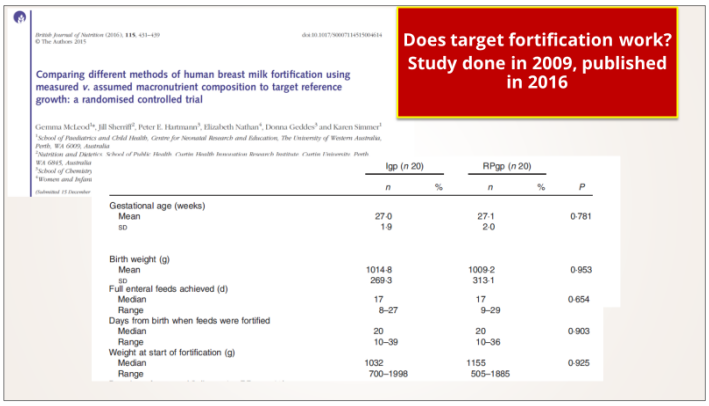
Slide 55 – Comparison of All Centers for High QC Fat



Slide 56 – Performance of Bedside Milk Analyzers can be Improved by Applying Principles of Good Laboratory Practice (GLCP)

Clinical Outcomes from Nutrient Research Studies

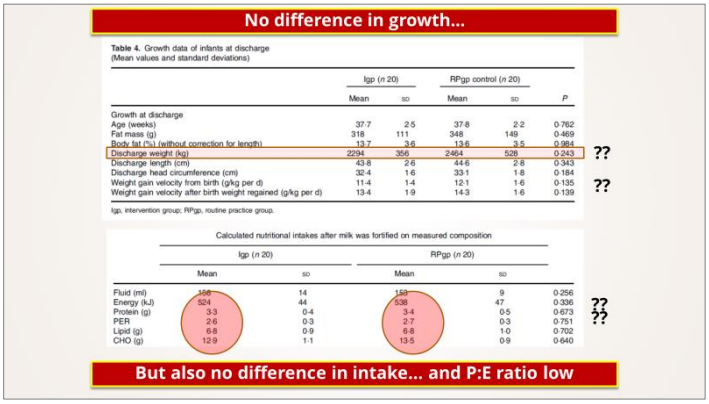
There is [a study] from Karen Simmer's group that was done in 2009 with an unvalidated device. She did it in about 20 babies,[26] and looked into individualized vs regular fortification, and was very disappointed they didn't find a difference. However, if you look into the data she provided about the energy and protein intake that babies got, then it was funny to see that both groups basically got the same intake. Maybe the goals that they wanted to achieve with nutrient intake in preterm babies were too low because there were no differences in both groups. There was no need to measure them because the normal milk fulfilled those criteria already, but they were too low.



Slide 57 – Does Target Fortification Work?

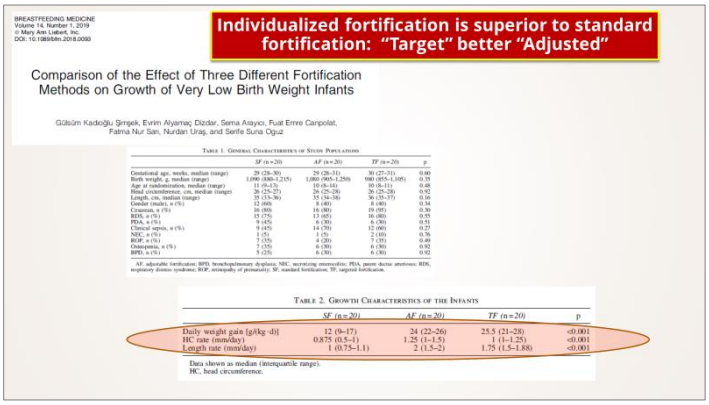
State of the Art: Precision Nutrition in Preterm Infants

If you look into the protein-to-energy ratio here [Slide 58], nowadays you would go with 3.3–3.6 PER, or 3.9 even, to achieve good growth in those babies.[27] That's why we need to place a question mark behind this study, unfortunately, from this great group.



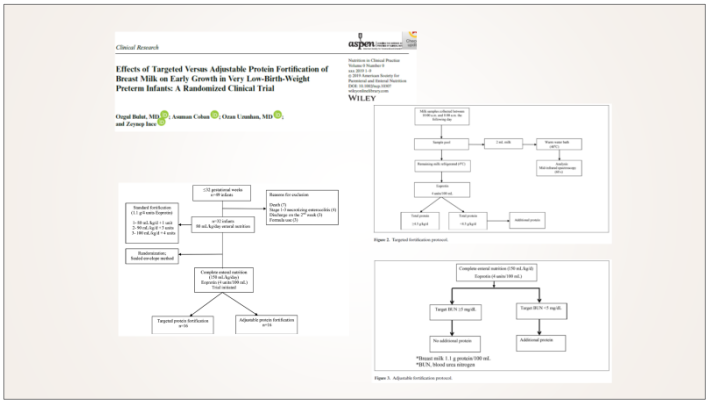
Slide 58

There are 2 more studies that have been recently published [Slide 59]. One is from [Zekai Tahir Burak Education and Research Hospital] Turkey.[28] They looked into standard fortification vs adjusted fortification vs target fortification and found that adjusted and target fortification did much better compared to standard fortification. The target fortification was a little better compared to adjusted fortification.



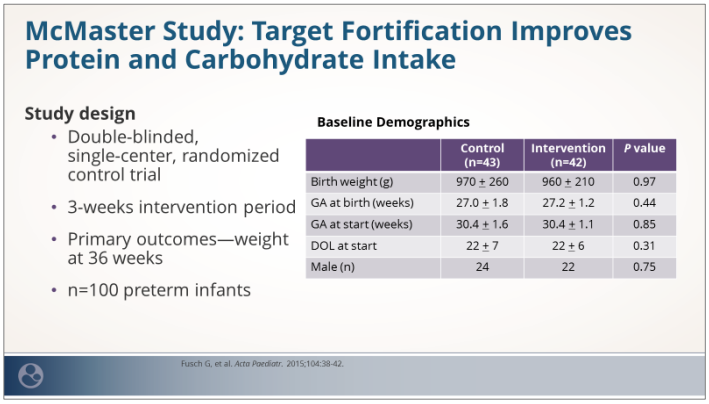
Slide 59

There's another study [Slide 60],[29] also from Turkey, only comparing adjusted vs target fortification, and they found that the target fortification was much superior compared to the adjusted fortification.



Slide 60

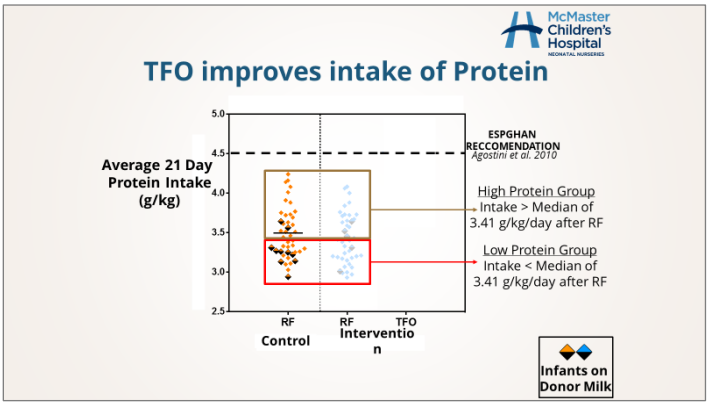
So, we [McMaster University, Canada] did a study ourselves over the last years.[30] It was a randomized, controlled, blinded trial. As you see [Slide 61], with babies of 970 g of birth weight and gestational age of 27 weeks. We measured human milk content three times per week, and then adjusted according to ESPGHAN recommendations. The primary outcomes were weight at 36 weeks, plus neurodevelopmental outcome.



Slide 61 – McMaster Study: Target Fortification Improves Protein and Carbohydrate Intake

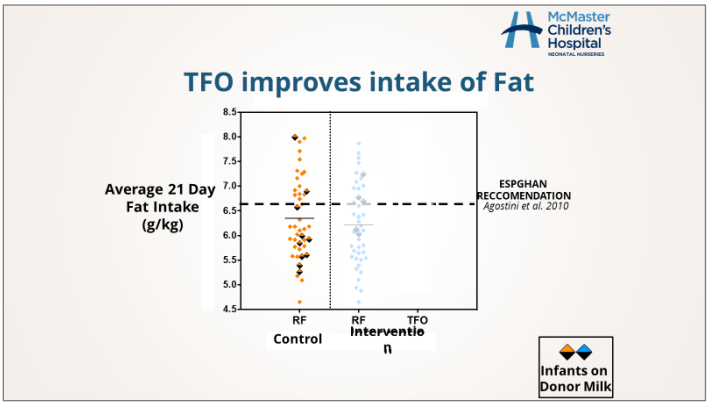
What you see [Slide 62] is the intake of protein. In the control, that is standard fortification. Intervention is the target fortification. After routine fortifications of standard fortification, both groups showed the same distribution, but after, target fortification showed improved protein content, and

the variability got a little smaller compared to the natural variability.

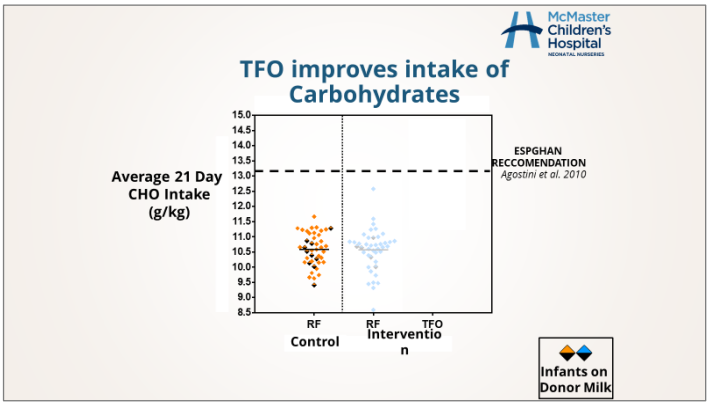


Slide 62 – TFO Improves Intake of Protein

It also improves the intake of fat, but the effect is not as big because North American fortifiers are heavily fat based, whereas European fortifiers are more carbohydrate based and do not put so much fat in. But carbohydrate intake was much higher in this group with the target fortification.

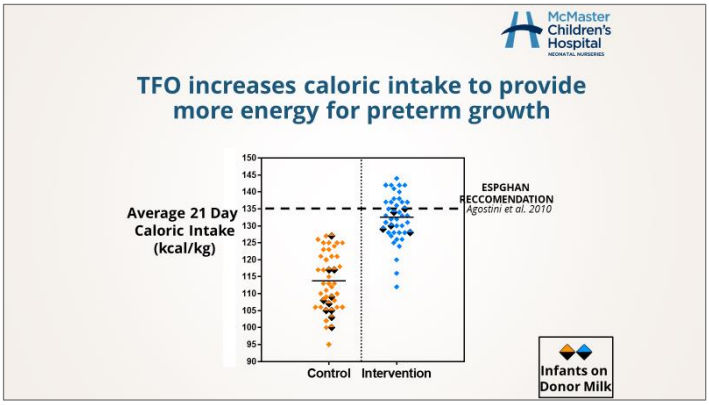


Slide 63 – TFO Improves Intake of Fat



Slide 64 – TFO Improves Intake of Carbohydrates

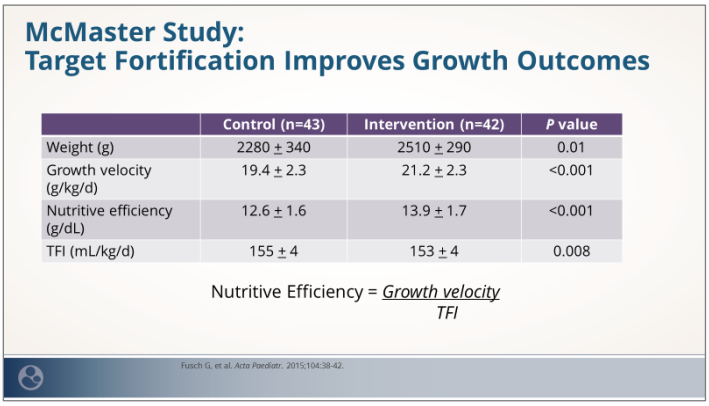
Overall, the energy intake was also much better.



Slide 65 – TFO Increases Caloric Intake to Provide More Energy for Preterm Growth

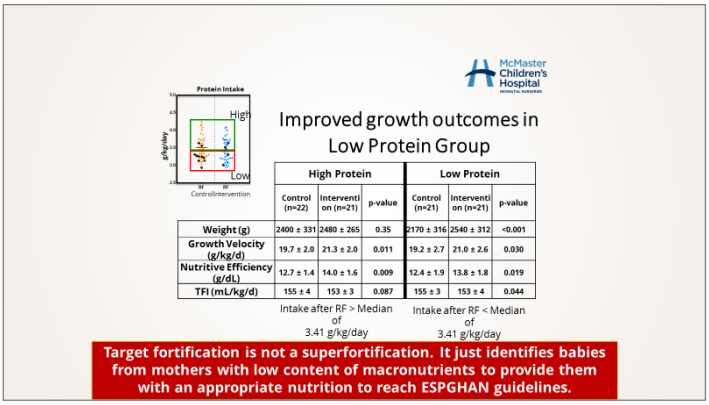
These are the results at 36 weeks [Slide 66], control: 2280 g, intervention: 2510 g. This is highly significant; the paper is submitted for review in a journal.

State of the Art: Precision Nutrition in Preterm Infants



Slide 66 – McMaster Study: Target Fortification Improves Growth Outcomes

We then looked at subgroups: those from mothers who have a high protein content and from mothers that have a low protein content. You see [Slide 67] that the effect between control and the intervention in the high protein group is not visible. That is not surprising because moms already have a high protein concentration. Whereas with the low protein group, the effect is really even bigger compared to the whole group. This is the group with the main effect.



Slide 67 – McMaster Study: Improved growth outcomes in Low Protein Group

The important thing is that target fortification is not a superfortification. It just identifies babies from mothers with low content of macronutrients to provide them with an appropriate nutrition to reach ESPGHAN guidelines.

We also have perinatal characteristics, and it was a trend toward better outcome. Interestingly, babies had a better food tolerance in the target fortification compared to standard fortification. Perhaps because the inflow was more constant compared to the variability, which is higher in the standard fortification group.

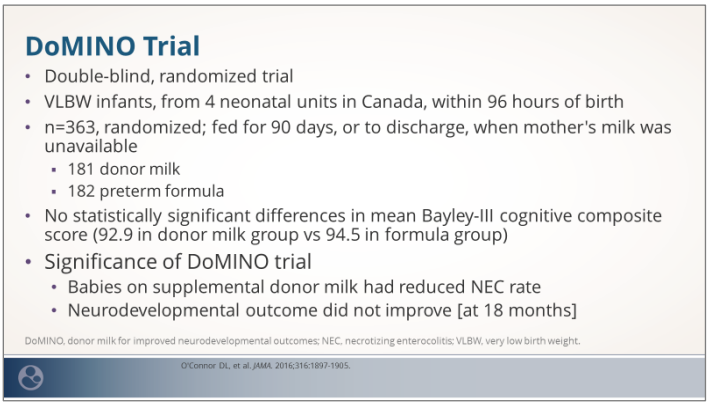
In terms of clinical chemistry, there was nothing very eventful. In body composition outcomes, babies increase their lean mass, but they also increase their fat mass; although, it was still proportionate.

We have 2 years and 18 months of neurodevelopmental outcome. We found the trend towards better neurodevelopmental outcomes, but it never reached statistical significance. We would have needed triple the number of babies to get something with this variability and with this difference that we found, but it looks very promising for larger trials.

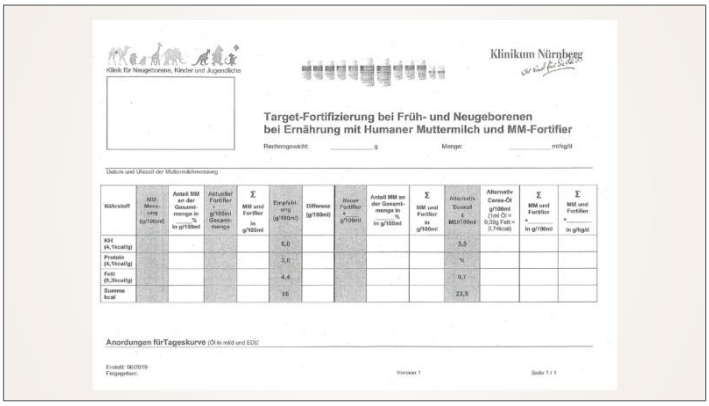
One last word to supplemental donor milk. Donor milk is very much propagated in [NICU] units now, so if the mom doesn't have enough breast milk, to avoid exposure to formula. However, the DoMINO trial from Deborah O'Connor, PhD, RD, from [The Hospital for Sick Children] Toronto where we [McMaster Children's Hospital] were also a test site, did show a clear benefit for sepsis and for necrotizing enterocolitis, but it was disappointing in terms of neurological outcome at the age of 18 months.[31]

This might be due to the fact that donor milk is even more protein-depleted because it's usually obtained late in lactation. We have found donor milk with 0.6, 0.7, 0.8 g protein/dL, which is far below the 1.1, 1.3 g/dL.

State of the Art: Precision Nutrition in Preterm Infants



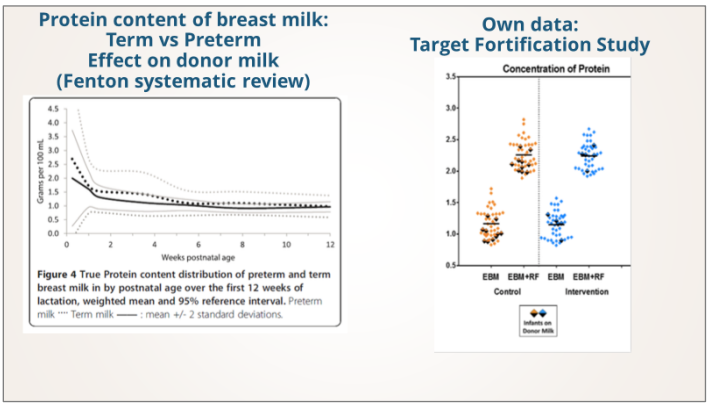
Slide 68 – DoMINO Trial



Slide 70 – Target Fortification Worksheet

Donor milk might need to be extra fortified, and not only by 0.3, but by maybe 0.5 g protein/dL to achieve proper growth. If we would do a trial with a little bit more protein and maybe measure the composition of donor milk, then we might achieve even a difference in neurodevelopment at the age of 2 years.

These are data are [Slide 69] from our own study.[32] You see the black diamonds are the donor milk, and they are usually lower in breast milk content.



Slide 69 – McMaster Study

This is a sheet that we use to calculate [Slide 70]. It looks complicated, but it is not.

The effects when you start to measure and care about breast-milk content is that staff develop interest in growth because they understand the nutritional physiology and expected growth patterns and trajectories. Growth in nutritional assessment becomes an issue in the [NICU] unit as part of daily routine, not only once per week (like some units). Staff get excited when they see the results of macronutrient contents and, together with the knowledge stated previously, calls for action.

It's comparable to blood-gas analysis. If you see a pCO2 [partial pressure of carbon dioxide] or 2 of 32 mmHg, then you adjust your ventilator settings before you see cystic lesions in the ultrasound weeks later.

In Summary:

- Postnatal nutrition and growth patterns of preterm infants have an impact on later somatic and neurodevelopmental outcome.
- Postnatal growth patterns are related to nutritional intake provided by neonatal staff.
- All staff involved in neonatal care should have an understanding of the basic physiology of growth and how nutrition is related to it.
- Individualized postnatal growth trajectories can be predicted and may provide a new reference point and support clinicians to guide

State of the Art: Precision Nutrition in Preterm Infants

growth of an individual infant ("Precision Medicine").

- Preliminary validation results appear reasonable.
- Postnatal weight gain [per kg/day] seems to be higher, by 10%, compared to fetal weight gain. (I couldn't elaborate on that, but it is in the papers we have published.)
- The current concept of human milk fortification is based on the assumption of an average composition of breast milk.
- Composition of breast milk is highly variable. This can lead to clinical conditions with insufficient or unproportionate intake of one or more macronutrients, thus compromising growth and later outcome.
- Individualized fortification is feasible ("Precision Medicine").
- Adjusted fortification may help to improve growth but is not efficient in all preterm infants. Data about MDI [Mental Development Index] are not available.
- Target fortification reduces the risk of postnatal growth restriction.
- **Important**: Target fortification is not providing "super" fortification. It identifies babies with mothers who "produce" breast milk with insufficient MN [macronutrient] composition and provides them with intake according to ESPGHAN guidelines
- Measuring only protein content might not be sufficient. Fat content is highly variable, due to the lactose content.
- Modern fortifiers should contain more protein (ca. 0.5–0.7 g/kg/d) and a more balanced mixture of fat and carbohydrates[33]
- Donor milk can be reliably measured. Pasteurization does not distort the analysis.
- For donor milk, additional supplementation using 0.3–0.5 g protein/100ml seems to be reasonable.[34]
- The optimum components for target fortification need to be developed. The fat-based concept of fortifiers available in North America to provide the extra calories needed should be reviewed.
- For both "high-end" fortification strategies modern modular components need to be developed to conserve the NEC protective effect of breast milk (cow's milk protein free) and minimize the pro-inflammatory potential (omega 3:6, limited MCT [medium-chain triglycerides]).
- Concept should be proven in a blinded multicenter RCT [randomized control trial], including body composition measurements and neurodevelopment outcome.

Question & Answer

Editor's Note: This is a transcript of audience questions together with Dr. Fusch's responses from the November 4, 2019, audio webcast.

How do you clinically implement milk analysis?

Christoph Fusch: You need to identify the right space and the right workflow. [It] maybe best to go into a [NICU] that is already doing it, to get an idea about it, because we frequently [think] it's too much work. Once done, it's not so much work. It is like doing blood-gas analysis when you ventilate babies. You need to provide the right space, and you need to teach the staff in the unit what to do with the values you get. They need to have an understanding about the underlying physiology, what the intake should be.

Then you need to work to get the right handling, because you can always have preanalytical and analytical errors, and get familiar with good laboratory practice.

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What do we need to think about and do in the NICU to develop a better understanding of individual baby needs?

I think we have a paradigm shift. Many, many years ago, if I may say, when we started neonatal medicine, we were talking about ventilation and back and forth and doing it the right way. I think there are many problems, they are not all solved, but respiratory insufficiency is less of a problem in preterm babies nowadays. Many more preterm babies survive, and more immature babies survive, and they also seem to survive in a better condition.

Now we have a responsibility to make them grow. The important thing is that we expand our knowledge from providing "intensive," intensive care, to this kind of developmental care by giving them the right amount of food, so they can grow the right way. Because, I personally believe that the effect size of making babies grow the right way—in terms of later neurological outcome—is very high. You need to develop an understanding of what the impact of nutrition is on a single baby, also to understand that it's not as spectacular as ventilating babies, but it's maybe as efficient.

How did you overcome the barrier of the high cost of the milk analyzer?

That's a good question. I talked to our administration and said, **if we can make babies grow better, there's a good chance we can discharge them earlier.** That sounds a little strange, but babies need to develop fat mass. Not too much, but a certain amount. This is part of the postnatal transition, as well. If they grow well, if I give them enough to eat—not too much—but if I give them the right amount to eat, then we have really nice growth curves. And, the baby becomes, in terms of thermal regulatory control, much more stable earlier. Then we can talk about length of stay and reducing costs. That is exactly what we see. We need to argue a little bit with [our] administration to give out the money because we are providing better care. A few days shorter of NICUs stays [saves] thousands of dollars.

Why are the NICUs in Europe using milk analyzers more often than the NICUs in the United States?

I don't know. There was no FDA-approved device, but there are now. Some were using it together with research studies. I would still encourage people to start using milk analyzers, to do it in a study, to control what you are doing, and that you are doing the right thing.

But that's the same in Europe, as well. I don't know exactly why it is not happening. Because I think there's more and more data coming out so it might work.

Are studies being done on mom's dietary protein intake and grams of protein available in the breast milk?

It comes down to the question, "with mom's dietary intake, can we influence the [breast] milk composition?" Unfortunately, there's nearly no impact of mom's diet to breast milk macronutrient content, which means lactose, fat, and protein. You can't eat 1 or 2 more steaks and get more protein in breast milk. That does not work. What happens is that fatty acids you eat (eg, fish oil), which appear also in breast milk, but it's not the amount.

Some vitamins [can help] influence, like vitamin A. If you eat more [vitamins], it also [appears] in breast milk.

There is one thing that impacts protein content, which is the body composition of the mother. That means that mothers who are a little more stable have higher [protein] content. Many mothers would like to lose weight at the end of pregnancy.

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According to you, Dr. Fusch, how important are micronutrients like omega-3 fatty acids, DHA, and ARA in fortification?

I think they play a role. But there are not too much data just right now on it, and also in terms of measurement, quick measurement. There's a certain problem, which is we can't usually do it at the bedside. There's not much data in terms of doing the same thing as target fortification. I cannot comment more on that, unfortunately.

What are the most common nutrients preterm infants lack?

In terms of breast milk, it's clearly protein and fat. Fat is underestimated (how low fat content can be in breast milk). Sometimes we have vitamin K, as well as a problem, but surely, we have a strategy for that.

Abbreviations

ADJ	adjusted fortification	**MDI**	Mental Development Index
AGA	appropriate for gestational age	**pCO2**	partial pressure of carbon dioxide
BMI	body mass index	**PreCES**	Preterm Contraction of Extracellular Spaces
BPD	bronchopulmonary dysplasia	**SGA**	small for gestational age
BUN	blood urea nitrogen	**STD**	standard fortification
DOHaD	Developmental Origins of Health and Disease	**TeCES**	Term Contraction of Extracellular Spaces
ELBW	extremely low-birth-weight	**TFO**	target fortification
		VLBW	very low-birth-weight

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