Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Early Metabolic Programming of Growth and Long-Term Health

✦ Course Transcript ✦

Editor's Note: This is a transcript of a live conference presentation on November 15, 2022. It has been lightly edited for clarity.

Berthold Koletzko, MD, PhD: What I would like to discuss with you is the global burden of disease and how we can influence that during early life. I will focus on postnatal metabolic programming and, if we have time at the end, try to give you a little glimpse into our ongoing research to explore underlying mechanisms.

Early Metabolic Programming

We all know we have a wave of noncommunicable diseases (NCDs) around the world, both in high and in middle- and low-income countries in Europe. NCDs cause 90% of deaths and 85% of years lived with disability. Now you may say, well, that's a problem of old age; that's not a problem of the beginning of life. Not so. We have a great opportunity to influence NCD risk at the beginning of life. Obviously, one of the key drivers is the epidemic of obesity where we've seen more than an 8-fold increase in 4 decades in childhood obesity. We have heard from the World Health Organization that we have preventive potential, particularly in 3 phases of life: during pregnancy and preconception—the very beginning of the first 1,000 days, during infancy and early childhood, and during adolescence, which, of course, involves the period of preconception.

This is the concept of early metabolic programming of lifelong health with the concept that environmental, and particularly nutritional cues during limited sensitive periods of developmental plasticity, have lasting effects on our body, its structure, the physiology, the function of tissues and thereby health, physical and mental performance, and long-term disease risk.

These are the 3 key programming pathways we are currently following based on the available evidence. There is the risk increase for adiposity, obesity, and related incidences by fetal over-nutrition related to maternal obesity, high weight gain in pregnancy, certain dietary patterns in pregnancy, gestational diabetes. I won't go into further detail here but will focus more on what happens after birth. Postnatal overnutrition—accelerated postnatal growth is a risk factor and the biggest of all is the mismatch pathway. The mismatch between low birth weight and rapid postnatal growth, which is a real killer, if you like.

Rapid weight gain after birth, in the first year and the second year of life, has been associated with an increased risk of overweight and obesity [shown] in a number of studies around the world. On the left panel, you see a compilation of studies that all show that children who have a high weight gain in the first and second year of life have an increased risk of obesity in childhood, adolescence, and adulthood. Overall, if you adjust for other confounders, there's almost twice the risk of obesity with high weight gain in the first 2 years of life. On the right, you see a large study from Germany showing very much the same. If you have a high weight gain, high body-mass-index gain in the first years of life, then your BMI remains higher, and you are more likely to have a high body mass index in adolescence and adulthood. In other words, those who grow fast early on have a higher risk of obesity later.

So, what our grandmothers believed, or least at least my grandmother believed, is wrong. My grandmother believed on giving the baby an extra spoon, make it chubby and round, make it look like a happy Buddha, so it's protected against the next

Early Metabolic Programming of Growth and Long-Term Health

infection. That's not what we want anymore because it predisposes [the infant] to risk later.

Early Rapid Growth Implications

We looked at the growth in 6,700 children where we had longitudinal data from affluent countries and did a cluster analysis to dissect different growth patterns. To our surprise we saw is that the normal growth, which is the growth we see in our percentiles, was only followed by half of these children. Only half of the children had a Z-score of the BMI of, more or less, zero. They were growing along the percentile. The other half, in blue, almost 48.5% had what we call early rapid growth, the same pattern that you've seen before with rapid weight gain the first 2 years of life. Then the BMI went slightly down again, but it remained elevated during school age. So, these are the children that have early rapid weight gain and then have a high risk of all-weight obesity at later ages. Then there's a very small group, 1.5%, with persistent rapid growth. You can say the hopeless group, if you like, who keep going up with their BMI continuously, [resulting in] the superobese children at school age.

Interestingly, we found this related to early nutrition. Children who were not breast fed or were breast fed less than 3 months, had twice the risk in the early rapid growth cluster, to be in this cluster, and 2½ times the risk of being in the extremely high-risk cluster, the persistent rapid growth. What's more, in the subgroup of individuals that we could follow until adulthood where we had data at 20 years [of age], you can see that not only their BMI but also fat mass and the fat-mass index is still elevated in adulthood. So, early growth clearly matters.

Now, why is that? Well, if a baby or a young child grows rapidly, it will not deposit more lean mass, more muscle mass, but will deposit more body fat. Increased body fat mass is then leading to reduced insulin sensitivity, higher insulin resistance, metabolic inflexibility, which is a key driver for hyperglycemia, hyperlipidemia, metabolic syndrome, and noncommunicable diseases.

This is a particular problem in those born small, our preterm babies, our low-birth-weight babies, our SGA [small for gestational age] babies. If you have a baby who has a slow fetal growth, a low birth weight, and then is exposed to a lot of calories, mother and grandmother are happy the baby is gaining weight fast— looks more like the neighbor's baby—then this baby will deposit a lot of body fat and will have an increased risk of adult adiposity, insulin resistance, and NCD risk. You all know that we have studies following up preterm infants long-term and show that, in many cases, the previously preterm-born individuals have higher body fatness at later ages. That is related, this change from a low weight to an increased body weight to a higher risk of NCDs, diabetes, obesity, myocardial infarction, and stroke.

Early Weight Gain Influences

So, can we do something about it? Is increased early weight gain just genetically determined or does early feeding matter? Well, you've seen already our cluster analysis before that suggests breast-feeding may be protective and that was also shown in this old study in California that is still valid, very meticulously done, where infants in California were followed prospectively from birth, if they were breast- and bottle-fed. Interestingly, their weight for length was pretty much the same during the period of exclusive milk feeding. But the curves deviate when the children were only partly milk-fed or not breast-fed at all anymore. They were significantly different from the second half of the first year onwards, and the bottle-fed babies stayed heavier at 1 year and 2 years of age. This is a typical example, in my view, of programming and early intervention that induces an effect that becomes apparent after the intervention.

Early Metabolic Programming of Growth and Long-Term Health

This difference in weight gain is associated with a difference in obesity. This was the first large study that we published more than 20 years ago looking at the relationship between breast-feeding and obesity. Later we looked at more than 9,000 children in the state of Bavaria in the south of Germany. And at school age, children who were breast-fed, compared to those never breast-fed, had a reduced risk of overweight and obesity, even after adjustment for all the confounders you can dream of (eg, sociodemographic, smoking of the mother, low birth weight, what have you). Perhaps even more convincing is that there's a dose-response relationship: longer duration of breast-feeding relates to a lower risk of obesity at early school age.

That was replicated in many observational studies around the world. Here you see the results of 5 different meta-analyses, and they all associate breast-feeding with a reduced later obesity risk in childhood and adulthood, with a 12% to 26% risk reduction. Now, that's not a lot for the individual, but for a population, it's huge. If you can prevent 1 in 4 or 1 in 8 cases of obesity by improved infant feeding, that's a huge public health benefit, obviously. The advertisement on the left is still true. Nurse the baby; it's your protection against trouble. I really like the last line as well: Consult your doctor if you have questions about infant feeding.

Early Protein Hypothesis

So, why is that? We thought 1 of the factors, at least behind this protective effect of breast-feeding, might be the higher early protein supply we used to give with bottle feeding, which we thought would induce higher weight gain and increased risk of later obesity. There is a lot of data to support this assumption. For example, this study in 600 mother/infant pairs where breast milk composition was measured at 1 time point at 1 to 2 months after birth, and the milk protein in this 1 milk sample. Milk protein content in early lactation predicted the body mass index of the child at 1 year of age. Milk fat did not predict. It was only the protein content of the milk that predicted the weight gain. As you see, the formula-fed babies had a higher BMI, and they also had a higher protein intake.

This relates to the early protein hypothesis we have followed. The concept that a higher protein intake could increase the secretion of insulin, raising amino acids, thereby enhance the secretion of insulin and IgF-1 [insulin-like growth factor-1], the key growth factors in infancy, promote weight gain, fat deposition and thereby, later, obesity. You see in the top panel, the intake of energy and protein of formula-fed babies in the 1990s compared to those of breast-fed babies. And you see that formula-fed babies get more energy at 3 and 6 months of age, but particularly they get a much higher protein intake, 1.6- or 1.8-fold higher than the breast-fed babies.

If you have a hypothesis, you try to test this with a double-blind, randomized trial. With infant feeding that's difficult, but we were lucky to get a lot of funding from the European Commission and performed this double-blind, randomized trial where we enrolled almost 1,700 healthy babies born at term, born in 5 countries: Spain, Italy, Belgium, Poland, and our country, Germany. We had more than 500 children who were breast-fed exclusively for at least 3 months. As you know, at the beginning, breast milk provides about 1 to 1.2 g per 100 mg of protein. Then we had more than 1,100 children who were randomized, double-blind at a median age of 2 weeks to either a conventional formula that was typical at the time, with high protein content, an infant formula of 2 g, and then in Europe, we give a follow-on formula with a reduction of complementary feeding, which had even more, 3.2 g of protein. On intervention formula, the same caloric density but less protein, more similar to breast milk, and more fat, so that the energy density was the same.

Early Metabolic Programming of Growth and Long-Term Health

The formulas were offered for the first year of life, then the intervention stopped and, after the first year, the children had exactly the same dietary intake. We followed up with these children through adulthood. We just published data at 11 years, and we're now performing the follow-up studies in young adulthood. There were no safety issues, fortunately. The children grew the same with the higher and lower protein intake. You see here 2 time points for the length, growth, tolerance, acceptance, lab safety markers, were all good with no safety concerns whatsoever. But there was an effect on the weight development. You see the body mass index at 2 and 6 years of age, and you see that with the conventional formula, with higher protein intake, the BMI is significantly higher than the breast-fed babies or the randomized group, which was getting lower protein in the first year of life. The protein intake in the first 12 months had a lasting impact on body size up to school age, and we now have data at 11 years and early adolescence.

Now, importantly, the effect on mean BMI was relatively small, but in the upper percentiles, in the 90th and 95th percentile, the effect was huge. With the higher protein, the percentiles were dramatically different, and therefore the occurrence of obesity at school age was dramatically different. In the previously breast-fed children, we had 3.5% obese children at 6 years, across the 5 countries. In the infants fed conventional formula, it was 10.5%. In the lower protein group, it was reduced to less than half, to 5.2%. If you adjust for other factors influencing obesity, the adjusted odds were an even 2.64 [%] reduced by giving less protein in the first year of life. This is a huge benefit in terms of long-term obesity prevention.

It was not only the body weight, it was also the body composition. You can see that from 2 years on, the children receiving more protein the first year of life were fatter. Up to school age and, again, up to 11 years, they have remained fatter. So, eating more protein doesn't build muscle, it builds more body fat, in this study at least.

The conclusions are very clear. Infant feeding has much more marked effects on later obesity. Breast feeding protects, which should encourage all of us to enthusiastically promote, protect, and support breast feeding. For all children, we should avoid a high protein supply. Infants who are not fully breast fed should get infant formula with less protein than previously, but that requires good protein quality and there may be further benefits in the future for improving that. Also, we should avoid cow's milk as a drink in the first year of life because cow's milk provides 3 times as much protein as human milk or modern infant formula. In fact, the ALSPAC [Avon Longitudinal Study of Parents and Children] study in the UK has shown that children who drank more cow's milk at the age of 8 months had the highest weight at school age, at 10 years. So, avoiding cow's milk seems to be an important contributor to reduce risk. That's what we go out to the public with our EU-funded project: no cow's milk in the first year of life.

Underlying Mechanisms

I would like to ask for your patience and give you a glimpse to explore underlying mechanisms a little bit more because I think understanding mechanisms is important to help us refine our strategies for intervention and come up with more targeted and more powerful preventive opportunities. One mechanism we have been looking at is the epigenetic modification of gene expression by early life exposures. We know our genotype is important for determining phenotype, but genotype alone doesn't do it. It's the expression of a gene, of our genes, that matter. We've now learned that environmental nutrition, particularly during sensitive early periods of development, change the epigenetic makeup, the biochemistry, of our DNA, and thereby the expression of genes. So,

Early Metabolic Programming of Growth and Long-Term Health

with the same genotype, we can develop very different phenotypes.

The most studied mechanism is DNA methylation. Cytosine, 1 of the 4 alphabet letters of our genome, is methylated. A methyl group is added to cytosine, which is always coupled with guanine. So, we have the CpG [Cytosine phosphatidyl Guanine] sites to a large extent dispersed all around the genome. We don't really know what they do, but less than 10% are in the regulatory regions of our genes. And if there, the CpG islands are methylated to a small extent, to a low level only, then transcription factors can bind well, and the gene is expressed. But if we have a high degree of methylation, then the binding of the transcription factor is blocked, and the gene is not expressed to the same extent. If you like, the gene is partly switched off.

So, we've looked at that, and I want to give you a couple of examples because we don't have the time. This is a meta-analysis we performed with 2 studies, the CHOP [Childhood Obesity Project] study that I showed you, and the Generation-R study that was done in the Netherlands. We looked at the effect of infant animal protein intake, dairy and meat protein intake, at the age of 1 year in relation to DNA methylation at the age of 7 to 12 years. You see, yes, the animal protein intake changes DNA methylation at school age. That doesn't demonstrate that this is really the response mechanism for the effects, but it suggests it might be one, and the next step, of course, is to look at the genes that are methylated and see what their physiological effects are.

We also have found that the DNA methylation predicts childhood fat mass. So, fatter children at school age in our CHOP trial have a change in specific gene loci in the degree of methylation. When we look at the function of these genes, we come up with exciting hypotheses on the potential underlying mechanisms.

The other question we looked at is the metabolic predictors, where we think we have particular opportunities for nutrition intervention because what we feed clearly induces directly the metabolic response in the baby. We've used a targeted metabolomics approach at Hauner in Munich, which is a very powerful technique where, basically, from a drop of blood, you can measure hundreds of metabolites and, in our case, also steroid hormones. So, you get a global picture of the metabolic state of the baby, you can relate it to exposures, such as different dietary aspects and to endpoints, for example, growth or body composition or other endpoints.

I want to show you a couple of examples to show you the power of this methodology. Here, we looked at a group of 250 pregnant women and their baby at the metabolome, the metabolic picture in pregnancy in the 3 different trimesters of pregnancy, and related this to the body fat content of the neonate, which clearly is related to body fatness in later ages and also to metabolic health. Without going into detail, I can share with you that there are very powerful associations with certain metabolites that predict, in pregnancy, the body composition of the baby at birth.

Birth Weight Prediction

We also looked at the prediction of birth weight. We know, of course, the birth weight of the baby is determined by maternal body weight. The heavier the mother is, the heavier the baby, on average. We can predict, just by prepregnancy BMI, about 6% of the variation of birth weight. If we add traditional markers, like blood glucose and blood lipids, the predictive power doesn't change. It's still 6.2%. But if we add the metabolome of the mother into this model, then we can more than double the predictive power to predict the birth weight, which clearly shows that the metabolic state of the mother in pregnancy is a very strong predictor of the child fetal growth.

Early Metabolic Programming of Growth and Long-Term Health

Another example is breast feeding. We've seen before that the composition of human milk, the protein content in human milk predicts the growth of the baby, and it contradicts the concept that breast feeding and breast-fed babies are a homogenous group. They are not. We have looked at a cluster model of the metabolic state of breast-fed babies at the age of 6 months, and you see that we find a number of different metabolic clusters of all fully breast-fed babies and, importantly, the major metabolic clusters at 6 months predict a very different growth until school age. The body mass index up to 6 years, we can predict in breast-fed babies by their metabolic clusters.

If we look in more detail, then we see that the human milk protein content, which we've seen before, is a predictor of weight gain development, predicts 1 important metabolite in infant serum, lysophosphatidylcholine, at 1 month, which is a metabolite we love because it's coming up again and again. It is the very same metabolite that is also the strongest predictor of weight gain in this group of 700 infants in our CHOP trial, and it is the one and only metabolite that, in infancy in our studies, predicts a risk of obesity at school age. We have a number of ideas why that is and what the metabolic mechanism behind that is, but that remains to be substantiated with further work.

Finally, I want to go back to this intervention where we reduce the protein, where we randomized infants to higher and lower protein intakes, and we looked at the metabolic effect. You see there is an effect, as you would've expected, in all the essential amino acids, and the branch-chained amino acids, valine, leucine, isoleucine…, they stick out. They are particularly markedly elevated with the higher protein supply.

Now, along with them, also their catabolites go up. You probably remember in biochemistry, your lessons of branch-chained amino acids are split and broken down to organic acids and enter the Krebs cycle, and we see these acylcarnitines reflect that metabolism going up along with the branch-chain amino acids. So, this is a metabolic pathway. Most of you probably didn't like biochemistry at medical school. You tried to sleep through the sessions, but it is still important. Leucine, isoleucine, and valine are broken down by the branched-chain α-ketoacid dehydrogenase, and they're a very important key enzyme.

When we relate the amino acids to these metabolites, we have an important finding. There is a linear relationship up to a certain concentration and then there's a break point, the linear relationship is lost. With the high amino acid concentrations, the breakdown products don't go up anymore.

What does it mean? We interpret this as a high protein intake exceeding the capacity of the baby to metabolically handle these amino acids, to break down these amino acids. By the way, we find the very same relationship at almost the same concentration for blood urea nitrogen, which also tends to go up to a certain range and then it doesn't increase any further. If that is so, I think all of us would agree we don't want to give babies more protein than they can metabolically handle.

With these little glimpses into ongoing research, I want to conclude. Early nutrition and metabolism markedly modulate growth, body composition, later health, performance, and disease risk. With respect to obesity, our study has shown that the risk of obesity can be influenced more by infant feeding than by any other preventive intervention that we know of in childhood, based on recent Cochrane analysis. Exploring underlying mechanisms may improve targeted and even more impactful preventive interventions, but already now with the evidence we have, we have the opportunity for implementation of better early nutrition practices to achieve great benefits, and also a large return of investment. If you think of the cost of childhood

Early Metabolic Programming of Growth and Long-Term Health

obesity, it's a huge return on investment that we can have.

I would like to thank you all for your kind attention and thank a great team of colleagues and friends at our university in Munich, and also our collaborators across Europe, to whom we are grateful for the fantastic collaboration. Thank you.

Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children	**IgF-1**	insulin-like growth factor-1
BMI	body mass index	**NCDs**	noncommunicable diseases
CHOP	Childhood Obesity Project	**SGA**	small for gestational age
CpG	cytosine phosphatidyl guanine		

Annenberg Center For Health Sciences
at Eisenhower
Imparting knowledge. Improving patient care.

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