Pediatric Nutrition
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TRANSCRIPT

Supplementing Micronutrients and Trace Elements to Improve Growth and Outcomes in VLBW Infants

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The take-home point I'm going to try to convince you to consider, or to do, is sodium and zinc supplementation as a part of your nutrition program. And I'm going to provide some data on why I think it's compelling, and you can decide if you think it's important enough.

The ESPGHAN guidelines not only provide us with details or goals for fluid, protein and macronutrients, but also for sodium delivery and phosphorus, iron, zinc, etc. Any trace element you might be interested in, they have given you at least a target range, based on the available evidence, to target. So again, I'm going to try to use these blue and yellow droplets to signify the differences between mother's milk and donor human milk. I mentioned earlier that targeting protein becomes very difficult and I sort of started to allude to the fact that it's incredibly difficult to replete all of these micronutrients. If you look at sodium, we're supposed to deliver 3 to 5 meq/kg/d, so that's 69 to 115 mg. Just quick math, 1 mEq of sodium is 23 mg. If you're trying to do the math in your head, that's how they come up with these numbers. Again, you need 630 mL/kg/d to supply just the minimum amount of sodium for a preterm infant if they're donor-milk fed.

What's interesting is that the content of maternal milk is really still a mystery, particularly when it comes to minerals and trace elements. We focus a lot on protein and fat and carbohydrates when it comes to analysis. Why? Because it's really easy to do, and we now have sophisticated bedside devices that can do that, but we really don't have a lot of insight into these minerals and trace elements. We reviewed the literature, pulled out almost 30 articles. Again, I would say nearly all of the articles predate the turn of the century and in higher income countries. There's sort of a smattering, particularly in the early 80s and then again around the turn of the century, with some caveats around underrepresentation.

This is the overall data. When we talk about preterm human milk, and this is all-comers, we're not talking about ELGANS. We're talking about less than 37 weeks. You can see some very clear trends when you summarize the data. We have a much higher content of sodium early on and that content declines over the first month of life. As you might expect, chloride follows suit. Zinc, which I'm going to focus on here, is pretty steady, generally speaking, over the first month of life, but it is poorly expressed. It's in a very small amount in all breast milk. And then, if you look at other things like calcium, phosphorus, magnesium, you can see that there's relatively no change across the first month of lactation. Again, with magnesium, these bars are pretty small, so there's very limited data. But you just get a sense of the things that do change and the things that don't change, right? So, as you're thinking about lactation stage, protein changes, sodium changes, calcium doesn't, but again calcium is poorly expressed into human milk. I'm going to try to convince you, in the next 20 or so minutes, that sodium and zinc are essential to good growth and easy interventions for most NICUs to accomplish.

If we go back to these guidelines and we focus on sodium, let me just back just so I can re-emphasize this, our goal, from expert opinion, is 3 to 5 meq/kg/d, but I would make the point in the parentheses that we are talking up to 184 meq/kg/d. So, 184 mg of sodium is 8 meq/kg/d and I'm confident that that is a rare number that most people are targeting when it comes to enteral nutrition. But the realization is that some infants may need very high amounts of sodium and I'm going to try to help you identify who those infants are.

I want to return to the data that I presented earlier. Again, just to remind you, these are 40 women or thereabout that we recruited, all less than 33 weeks. The mean gestational age 28 weeks with about half of those infants being less than 28 weeks, what I consider to be extremely low gestational age, newborns or ELGANS. And again, two-thirds are Black, so we did have some race dynamics to take into account. If you look at sodium, for example, this is the whole cohort. If you look at all infants less than 33 weeks, you can see that, as I showed earlier, the sodium content in preterm milk does decline over time. It starts at roughly 30 mg/dL, so you're talking about 1 to 1.5 mEq per 100 mL. If you, again, have that 150 mL/kg in your mind, at that concentration you're delivering about 3, maybe just under 3, mEq of sodium per kilo per day at 150 mL. But, as you can see from this graph that the sodium content generally declines, although with the arrow bars widening, there is some heterogeneity in those relationships.

What's interesting is that if you look at the cut-off of 28 weeks, so we take all the infants less than 28 weeks and those above 28 weeks, you can see some really clear differences. The infants who are most vulnerable, those less than 28 weeks, the milk that they're provided from mom all have about 25 mg/dL or about 1 mEq per 100 mL. So again, if you're providing unfortified milk, you're looking at about 1.5 meq/kg/d at 150 mL/kg/d. And if you look at older preterm infants, they are getting much more sodium across that first month of life. While there are some trends to be had when you look at the whole dataset, I think we're missing some key insights into the particular vulnerabilities around infants at 28 weeks and below. And that gray zone is, again if we're targeting 150 mL/kg just for simple math's sake, you need about 47 to 76 mg/dL to get that 3 to 5 meq/kg. I know that's a lot of mixing of the math, but essentially that gray line is where we need to be. If we want to meet that 3 to 5 meq/kg/d, we need to be in that gray space for each of these graphs.

Of all the infants we looked at less than 28 weeks, no infant was receiving milk that had 47 mg/dL of sodium. So, zero at less than 28 weeks. So, it is a rare event that very small babies are getting sufficient amounts of sodium from milk alone. If you do the same comparisons looking at early and late, again these are the whole cohort compared to donor human milk, you can see there are some mothers who actually produce quite a bit of sodium in their milk, but the vast majority produce somewhere around 30 to 35 mg/dL. So, somewhere around 1.5 mEq per 100 mL. Donor milk is almost entirely deficient in sodium. It is, on average, 10 to 11 mg/dL, that is .5 mEq per 100 mL. So, if you are, again, providing 150 mL of straight donor milk, you're giving that infant less than 1 meq/kg of sodium. And so, again, sodium can be pretty significantly under-supplied when we're talking about donor human milk. And again, if you take our infants less than 28 weeks and you compare those infants to donor human milk, you can see pretty stark differences that none of those infants are getting adequate sodium just from the milk alone. So, I want to just emphasize that point. If we're talking about who's the most vulnerable to slow postnatal growth, it is our smallest babies and these babies are not only missing out on protein and we have fortification strategies and a lot of research sort of highlighting the importance of protein. They're also missing out on sodium and we need to be thinking about additional sodium.

Here is the same figure I'm trying to sort of land the plane on. If we're trying to meet the minimum sodium supply at 3 meq/kg/d at 150 mL/kg/d, we're going to come up a little bit short with early preterm milk, but we're only going to be delivering about 40% to 50% of that supply when we talk about later lactation, mother's own milk, and almost no sodium when we're talking about donor human milk. So, we're missing out on significant amounts of sodium, particularly with those infants provided donor human milk. But we have fortifiers, right? And we have the opportunity to fix this problem in some situations. If you look at our available fortifiers, liquid, commercial, human milk fortifiers, if you look at 24 kcal/oz, an equivalent caloric density, and we take less than 28 weeks' infants in the blue circles, greater than 28 weeks in the blue squares, and then donor human milk-fed infants in the yellow circles. You can see that some of these scenarios, you end up in this gray zone where you can provide 3 to 5 meq/kg of sodium. Again, the human milk HMF, in pretty much every scenario you provide adequate amounts of sodium per the expert guidelines. If you are talking about early and late or young and old, you can really struggle in some scenarios with certain human milk fortifiers and particularly with donor human milk. In our unit, we have chosen to supplement 1 to 2 meq/kg of sodium citrate beginning on feeding day 10. When they've established feeds at 100 to 120 mL/kg, every infant gets 1 to 2 meq of sodium per kilo per day. That is how we practice. We feel pretty strongly about this and we feel like it has made a substantive difference in the way that we care for infants in our nutrition program. I will say there is good data to suggest that particularly the ELGANS, so this is less than 28 weeks, will maintain a negative sodium balance out to 32 weeks corrected age.

If we think about an infant born at 22 weeks and they are receiving a low amount of sodium in their enteral nutrition, particularly as they transition off of parenteral nutrition, it may be 2 months before they start to accumulate sodium in an adequate amount. If you talk about why infants might be at risk for slow growth, this loss of sodium, plus the failure to deliver adequate amounts of sodium, I think is a part of that story.

Sodium supplementation in RCTs has been well studied and the evidence is pretty compelling I think. This study was just published this summer. Double-masked RCT in India. Again, 25- to 30-week infants, enteral feedings of 100 mL/kg. All of those infants were randomized to either 4 meq/kg/d of extra enteral sodium or a placebo that contained .1 meq/kg of sodium. So, essentially, the placebo has no sodium. They were not randomized if their serum sodium was greater than 145 at the time of randomization. Again, we're talking about kids who have a normal or low sodium in the serum and getting 4 meq/kg/d or zero. And then they did have a correction factor for infants when they achieved what they considered hyponatremia at 135, they would replenish with 3% sodium chloride.

Here's the data essentially summarized. In the yellow is the intervention and in the purple is the control. And you can see very clear pattern differences as infants proceed past the third week, such that the growth velocity which is how many g/kg/d you're obtaining over those time points. You can see that, in the yellow, we quickly rise to a max of just north of 20 g/kg/d and we maintain an average, over the 6 weeks, of somewhere around 18 to 19 g/kg/d, whereas the control group was under 15 g/kg/d. We're talking about a difference of 3 g/kg/d across 6 weeks. Now, that adds up.

If you look at other things, like length velocity, those kids who got sodium were longer across the 6 weeks and the incidence of hyponatremia was not nonexistent, but it was much reduced. In this cohort, again less than 30 weeks, two-thirds of those infants experienced a sodium less than 135. It is a common problem that affects easily two-thirds or more of our preterm infants. And this protocol, with extra sodium, enteral sodium, beginning at 100 mL/kg of feeding, reduced that number by half.

They are not alone in this study. If you look at a couple of RCTs that have been published before that, you can see that, on average, the weight difference between the intervention and the control group is about 3 g/kg/d. Iowa has published a couple of things and shown very similar differences in retrospective cohorts. And if you take the aggregate from the Petersen study in 2024, again doing sodium supplementation, you can again see very consistent patterns retrospectively in those infants who are fed extra sodium vs those infants in what is considered a placebo or control group. It takes a couple of weeks to see the differences arise, but they're not insignificant. And again, my goal is to figure out what are the easy things I can do, what are the low-hanging fruits in my nutrition program that I can accomplish with minimal impact on personnel, minimal cost to my unit, and I think sodium supplementation fits that goal.

Going back to our fortification strategy again, all of those studies used 4 meq/kg/d and that was on top of fortified human milk. If you're starting to follow along, we're talking about high amounts of enteral sodium being delivered. Again, I showed you this chart with the differences between the Prolacta, Enfamil and Similac fortifiers, again trying to target this recommended range of 3 to 5 meq, sorry, mg/dL. This gives us that 3 to 5 meq/kg/d. If you add 4 meq of sodium to every infant in this chart, you can see where those numbers land. We're talking somewhere in the neighborhood of 6 or 7 meq/kg/d of sodium in all of these studies. While the experts are recommending 3 to 5, and I think we have been using those numbers for generations now, it may in fact underrepresent what we actually need to be giving, particularly to the very smallest preterm infants. I do think sodium supplementation appears to be very safe. We're probably underappreciating how much sodium particularly our smallest babies need and it would be helpful to sort of leverage what is known now with a couple of RCTs and a handful of retrospective analyses to try to push those numbers up a little bit. Again, if we sort of take these estimates, we're probably undershooting and 5 might be more of the minimum number that we should be targeting.

I mentioned sodium here. I want to turn my attention to talking about zinc. If you look at the ESPGHAN guidelines, they recommend 2 to 3 mg/kg/d of enteral zinc or zinc supplementation and preterm milk has one-tenth of that amount. So, you're definitely going to fall short if you're trying to deliver 2 mg/kg of zinc with just looking at zinc in human milk. Again, a very similar schematic. This is the content of zinc over time and zinc is very connected to lactation stage. There's a nice review showing there's really not a lot of difference in zinc content by gestational age, but zinc definitely diminishes with lactation stage. And if you look at the MILQ Consortium, this acronym is Mothers Infants and Lactation Quality Consortium, that was published just this year. They've got really nice scatter plots and some median values for all of the nutrients. These are great references, representing moms from all over the world, too. I know that a lot of what we've talked about is the experience in North America, but this is a very good representative dataset for infants across the world.

Zinc, very highly concentrated in early milk, diminishes rather quickly over the first 30 days and then sort of levels out, but continues to decline over the first year of life. If you look at zinc by early vs late and compare that to donor human milk, there's no real difference apart from just the natural tendency of zinc to decline with lactation stage between early and late preterm milk. But there is a statistically significant difference in zinc content with preterm milk compared to donor human milk, but again none of those come even close to that gray area which is going to be the target zone for delivering that 2 mg/kg of zinc that we're trying to target.

We're trying to hit 2 mg/kg/d of zinc at 150 mL/kg/d and you can see that we fall well below that. In fact, donor milk and late preterm milk don't even come to the halfway point in those targets.

If we think about fortification, early mom vs donor human milk, with some of the fortifiers we can come close to that gray zone and then donor human milk really falls short in almost every respect. And then, importantly, the binding of zinc to casein and protein is high, so casein sort of pulls zinc in and holds onto it. Oftentimes it fails to be released into the intestinal tract.

Depending on the fortifier's main source of protein, you can have some issues with just releasing zinc and having it be bioavailable. Again, even though you're seeing the delivery mechanisms be a bit different, the quality or the type of constituents within those fortifiers may dictate how much zinc is actually bioavailable. We provide every infant in our unit, beginning on the same feeding day 10, 1 mg flat of zinc per day, not per kilo, just 1 mg flat, and we do that with zinc sulphate.

This is the review that the group out of Europe produced this last year. It's an excellent, excellent review, a lot of compelling data. I didn't go into the RCTs with zinc, but suffice it to say they're compelling in a lot of respects. A meta-analysis of 8 RCTs with about 750 kids showed that randomization to a zinc supplement increased weight, length and had higher motor development scores at 2 years of age. And then a separate meta-analysis of almost 600 kids showed reduced mortality with zinc supplementation. Again, what are the easy, low-hanging fruit that we can grab onto that are going to make a difference? I think zinc supplementation's an easy one to do once a day and it can make a pretty substantial difference in your nutrition program.

What about other nutrients? Magnesium, calcium, iron and D3, here are the scatter plots from the MILQ study. These are all available in *Advances in Nutrition* in the last year. Again, with HMF, you're providing somewhere around 8 to 9 mg/kg/d of magnesium and 120 mg/kg/d of calcium. Those are well within the respective guidelines from ESPGHAN. If you're talking about iron, the HMFs do not supply an adequate amount of iron and so you're going to have to provide additional iron as a supplement. And then again, D3, not enough D3 with fortification, so you're going to have to supplement those. Again, the idea that you're going to get by with just human milk or even fortified human milk is probably a misnomer. We need to be thinking about easy, low-hanging fruit to round out the nutrition value.

Let me just close on sort of rare earth things that we don't know a whole lot about. So, selenium. Selenium, in 2 RCTs, both in this century, appears to be beneficial in preventing late-onset sepsis. It has a role in helping neutrophil function and anti-inflammatory properties. Again, at 5 to 7 mcg/kg/d or 10 mcg flat per day, there was reduced incidence of late-onset sepsis. In PN, we get adequate amounts of selenium. The problem is HMFs are not a great source of selenium. If our goal is somewhere around 10 mcg/kg/d, preterm milk has about one-tenth of that concentration and then you're adding in HMFs that don't provide really significant amounts of selenium. So, we do not supplement with selenium, but I do think there's probably some research to be done on whether or not routine selenium or adding selenium to our HMFs or trying to encourage our partners in industry to think about this more might be helpful.

Manganese, another rare element. It is concentrated in TPN and this would be more in Amy's wheelhouse, but one of the issues with manganese is that it can accumulate in the basal ganglia of preterm infants and there's been good studies to show that accumulation can be detrimental. It's particularly true with prolonged TPN use because manganese is seen as a contaminant of many products. And there's really not been a lot of studies on this except for one very small RCT where they provided TPN that was depleted of manganese and they essentially showed that manganese levels in the plasma were similar between those infants who had manganese-depleted TPN vs those who had standard TPN. The point of that study is just to say I think we can get by without supplementing manganese. We get plenty of it in diet and as a leftover in fortifiers and other agents, so probably not something we should be looking to supplement. In fact, I think supplementation might prove detrimental. Again, our goal is like 15 mcg/kg/d. Preterm milk does have some. HMFs have some as a part of the processing. So, we probably deliver plenty of manganese.

Finally, I'll close with iodine. This is important for thyroid hormone production. At one time, we were talking a lot about iodine swabs and whether or not those were safe in preterm infants, but not a lot of RCTs about supplementation. There was one looking at whether 30 mcg/kg/d was necessary to meet the recommended delivery, but there was no difference in the placebo and the intervention group when it came to actual T4 and TSH values or on neurodevelopmental outcomes. Whether we should be giving more iodine or not is sort of up in the air. Using it as a marker for a hormone that has a self-regulatory component may not be the best primary outcome. But again, it's hard to know how you measure thyroid function apart from T4 and TSH in a simple way. Again, the goals for delivery from ESPGHAN are 11 to 55 mcg/kg/d, pretty broad range. Preterm milk gets you at least in that range and then the fortifiers add onto that. But again, bovine HMFs do not provide iodine, so it's only the human milk HMF where you're getting iodine. Preterm milk has iodine in it. You have to think about what are you missing out on, depending on your fortifier choice.

With that, I'll close with a couple of takeaways. I hope I've at least made a somewhat coherent stake on sodium supplementation. I think the idea that sodium should be limited in those first days after birth, right? We want those preterm infants to diurese and get rid of all that free water and regain that birth weight. And then, as they're establishing feeds, I think thinking about adding in a meq or 2 of sodium every day, sometime around the

second week of life, is helpful if, for no other reason than preventing hyponatremia and promoting a positive sodium balance in those preterm infants. And then zinc supplementation, again 1 to 2 mg/d will really help you get into those goals, target goals for ESPGHAN. Really clear data on zinc when it comes to mortality risk and improved growth. In fact, worldwide, zinc deficiency is a higher cause of mortality than iron deficiency if you look at the WHO's causes of mortality worldwide. Zinc is an important element that we need to be thinking a bit about.

The reality is that we probably can overdo it with zinc, since zinc can reduce copper and other 2+ cat ions, we want to get in that goal range. Some RCTs have supplied as much as 10 mg/kg/d which is a pretty decent amount of zinc and settling out somewhere around 1 to 2 seems like a good place to start. And, with that, I'll close.

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