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Sodium intake in very low birth weight infants: is more always better?

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The problem of sodium balance in low birth weight infants

In this issue of Jornal de Pediatria, Tanaka et al. publish results of their detailed study to assess the influence of fortification of banked human breast milk feeding on urinary fractional excretion of sodium, specific gravity and osmolality.[1] To our knowledge, no study in very low birth weight infants to date has examined strict sodium balance in this premature population first achieving postnatal growth with enteric feeding of human breast milk. The authors assume, and I think correctly, that human breast milk is the best nutritional resource for feeding premature human babies.

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However, some controversy still exists regarding the efficacy of human milk fortifier [in this study, FM85™ (Nestle) at 5 g per 100 mL of breast milk providing an additional supply of 1 g of protein, 3.4 g of carbohydrates, 20 mg of sodium, 75 mg of calcium and 45 mg of phosphorus]. While bone mineral content may be increased to values comparable to those in term infants with fortification, follow-up at 44 weeks postconceptional age was not affected by previous mineral supplementation.[2] Indeed Tanaka et al. state in their discussion, "the parameters evaluated are basically restricted to calcium, phosphorus, alkaline phosphatase and urea. Rarely is serum sodium evaluated." And their own data do not demonstrate significantly enhanced growth rates resulting from breast milk fortification, nor did they propose to evaluate bone mineralization as the result of breast milk fortification.

Rather, the authors raise their "concern with the potential adverse effects of diet on the renal function of preterms …, since the point of renal maturity is at around 34 weeks' gestational age, and it is premature infants younger than this who require fortified breast milk. The renal function of premature infants is faced by a variety of limitations, the most significant of which are: glomerular tubular balance dysfunction, characterized by a low glomerular filtration rate and an even more accentuated reduction in tubular reabsorption capacity, elevated fractional sodium excretion (FENa) and limited urinary concentration capacity."[3,4]

Sodium balance during fetal life and with premature birth

During fetal growth, urine volume formation is relatively low due to a low GFR associated with high renal vascular resistance *in utero*.[5] Fractional reabsorption of filtered sodium increases with maturity so that urine is hypotonic relative to plasma by mid-gestation. Urine formation again decreases towards term (past 34 weeks' gestation) as the distal tubules become more responsive to fetal arginine vasopressin.[6] This coincides with the transport of large quantities of sodium chloride and obligate water into the fetus from the mother *ensuring a positive water and electrolyte balance for growth*.[6,7] However, studies in fetal lamb preparations suggest that the by mid-gestation the fetus will respond to extracellular volume expansion with modulation of these high rates of proximal and distal tubular reabsorption.[8]

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Term infants continue to demonstrate positive sodium balance over a wide range of sodium intakes.[7] This characteristic of neonatal renal function *is favorable during active growth* and may be maintained by high circulating levels of aldosterone.[6] This functional hyperaldosteronism is probably a result of a blunted negative feedback control on renin production.[9] Despite its functional advantages for the *healthy growing infant*, the renal bias toward sodium reabsorption may limit the infant's ability to enhance sodium and water excretion during acute extracellular compartment loading.[10,11]

Premature infants have other difficulties with sodium balance. In contrast to the term infant, their basal excretion of sodium is high (reflected by a high fractional excretion of sodium at earlier gestational ages). With only a slight increase in GFR from *in utero* levels before 34 weeks' gestation, a relatively large percent of the filtered sodium chloride is excreted due to the less mature tubular response to aldosterone and diminished adrenal production of aldosterone in response to renin-angiotensin stimulation. Thus, the premature infant early in life is susceptible to both sodium wasting resulting in body water contraction, and an inability to accommodate salt and water volume expansion due to the limited GFR.[10]

Salt restriction versus salt maintenance in low birth weight infants

Costarino et al. conducted a randomized controlled trial of sodium restriction *versus* maintenance sodium administration during the first five days of life in infants born with less than 1,000 grams and less than 28 weeks' gestation.[12] Infants were randomly assigned to receive either no maintenance sodium additive, or sodium replenishment at 3-4 mEq/kg/day added to maintenance fluids beginning on day 2 of life. Two of 9 infants in the sodium restricted group became hyponatremic with serum sodium concentrations less than 130 mEq/L, while two of eight infants in the sodium replenishment group became hypernatremic with serum sodium greater than 150 mEq/L. Daily assessments of serum sodium concentrations were significantly and consistently higher in the sodium supplemented infants.[12] In Tanaka's study, infants were older, entering a growth phase, and did not demonstrate disturbances in reported serum sodium concentrations.

Sodium output in the urine remained the same for restricted infants early in the (Costarino) study,[12] but began to increase after day 4 in infants in the supplemented group. Sodium balance was nearly zero in the sodium supplemented group (intake matched urinary excretion), but remained negative in the sodium restricted group up to -6 mEq/kg/day. Fluid intakes prescribed independently of prescribed sodium intakes were similar in both groups of babies between 90 and 130 mL/kg/day. However, volume intake exceeded 130 mL/kg/day after 3 days in the supplemented infants, higher than the salt restricted babies who only received approximately 90 mL/kg/day. Urine output was fixed at 2-4 mL/kg/h (about 50-100 mL/kg/day) throughout the study in both groups, and was not dependent on either the volume of fluid administered or the amount of sodium intake prescribed. Tanaka et al. did not render calculations of actual sodium balance, and instead reported spot urine fractional excretions of sodium (one of the best indicators of renal tubule function in premature neonates), and measured urine osmolality and specific gravity as clinical indicators of solute loading. This editorial reviewer agrees these are reassuringly normal in the authors' study of pooled human breast milk with fortification in still very immature kidneys at < 34 weeks postconceptional age and followed in a longitudinal fashion over 3 critical time intervals.

Survival (in the Costarino study) was similar in both groups, and the occurrences of intraventricular hemorrhage and patent ductus arteriosus were also similar.[12] There was a trend, however, towards infants developing bronchopulmonary dysplasia in the high sodium/high fluid intake group: 7 of 7 infants *versus* 4 of 8 infants in the low sodium/low fluid intake group.

Hartnoll et al. observed that the increased risk of continuing oxygen requirement in extremely low birth weight infants is more likely to be a direct consequence of persistent expansion of the extracellular compartment and increased pulmonary interstitial fluid, resulting from sodium intake. This adds further weight to the authors' view that the timing of routine sodium supplementation should be delayed until the onset of postnatal extracellular volume contraction, marked clinically by weight loss.[13]

Neither the Costarino nor the Hartnoll study addressed sodium supplementation and renal salt handling in growing well premature babies, whereas Tanaka et al. address this significant question.[1] Apparently infants in Tanaka's study were well, and free of significant pulmonary disease. Therefore, sodium fortification would not have adversely affected their pulmonary function. In short we agree with the authors' conclusion, "No adverse effects on the renal function of these preterms were detected as a result of being fed fortified donor human milk."[1]

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The Latin American exception: why is childhood asthma so prevalent in Brazil?

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Ten years ago most researchers in Western countries "knew" what caused asthma, and we knew how to prevent it.[1] Asthma was an atopic disease caused by allergen exposure. The fundamental etiological mechanism was that allergen exposure, particularly in infancy, produced atopic sensitization and continued exposure resulted in asthma through the development of eosinophilic airway inflammation, bronchial hyper-responsiveness and reversible airflow obstruction.

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This Eurocentric view of asthma etiology was in fact never strongly evidence-based.[2,3] Less than one half of asthma cases are attributable to atopy and/or eosinophilic airway inflammation[2] and (non-allergic/non-atopic) neutrophilic airway inflammation may account for the other half.[4] Furthermore, although there are some clear cases of allergen exposure causing asthma in adults in the occupational environment, overall there is little evidence that allergen exposure is a major primary cause of asthma[3] and even some evidence that allergen exposure early in life may have a protective effect.[1] Certainly, allergen exposure does not appear to be the major primary cause of asthma that it has been assumed to be, nor to account for global patterns, or the striking increases in prevalence over time.[5]

As the "established" asthma risk factors are increasingly being called into question, epidemiological studies are playing a major role in the search for new theoretical paradigms which are more consistent with the epidemiological evidence and which have greater explanatory power. In particular, the "hygiene hypothesis" has been prompted by the results of several epidemiological studies showing that overcrowding and unhygienic conditions were associated with a lower prevalence of atopy, eczema and hay-fever although the evidence for asthma is less consistent.[6] An increase in microbial exposure and infections has been proposed as an explanation for these findings.[7]

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