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TABLE OF CONTENTS

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What We Know, Think We Know, or Are Starting to Know

Although we typically refer to micronutrients as a broad category, the division between vitamins and minerals is important. Vitamins are *organic* compounds, i.e., consist predominantly of the elements carbon, hydrogen, nitrogen, and oxygen. Conversely, dietary minerals are *inorganic* compounds, i.e., chemical elements other than the organic compounds, that are required to support life.

Within the class of minerals, some may be categorised as "trace minerals", meaning they are required in relatively small amounts to support optimal health and physiological function. Iodine is one such trace mineral for which deficient intake is considered by the World Health Organisation [WHO] to be the most preventable cause of brain damage on a global level [(1)].

Iodine deficiency results in a spectrum of adverse effects on human growth and development, known collectively as 'Iodine Deficiency Disorders' [IDD] [(1,2)]. But why a is trace mineral such as iodine related so strongly to neural growth and development? The reason is that in developmental phases, both during gestation and into infancy, thyroid hormones are required for neuronal growth [(2,3)].

Thyroid hormone function is, in turn, dependent on adequate dietary intake of iodine, and up to 80% of iodine in the body is stored in the thyroid gland [(2)]. However, because the developing foetus cannot produce its own thyroid hormones until after the first trimester, it depends on maternal levels of thyroid hormones [thyroxine or 'T4' in particular] to support growth and development. T4 production increases by ~50% in early pregnancy to support both maternal and foetal requirements, which in turn requires additional iodine.

Iodine requirements are significantly increased during pregnancy and lactation, for three primary reasons. The first is, as stated, the increase in maternal T4 production requires additional iodine [(4)]. The second is that, after the onset of foetal thyroid hormone production, the foetus requires its own iodine for production of T4 [(4)]. The third is that during pregnancy, alterations in kidney function increase the clearance of iodine from the body [(4)]. Collectively this increases the general adult recommended intake from 150mcg/d to 250mcg for pregnancy and lactation.

Consequently, maternal iodine intake is crucial. However, insufficient iodine intake is common in pregnant and lactating mothers, even in countries with mandatory policies of iodine fortifications in salt [(5–7)]. This may correspond to low iodine status of breast milk in exclusively or predominantly breastfeeding mothers, translating to low iodine status of their infant child [(4)].

Few studies have investigated the associations between maternal iodine status, feeding method, and thyroid hormone status in offspring, and the present study conducted such an analysis in a Norwegian cohort.

The Study

The present study was a secondary analysis of a randomised controlled trial [RCT] in 137 pregnant Norwegian women followed from 20-weeks gestation. This secondary analysis included the children born to the mothers who participated in the parent RCT, and the mother-infant pairs underwent follow-up visits at 3, 6, and 11-months postpartum.

Each follow-up visit included urinary samples from mother-infant pairs, breast milk samples from mothers, assessment of feeding method, and dietary assessment of mother-infant pairs. Infants were characterised according to the following feeding methods:

- Breast-fed, i.e., Exclusively or predominantly breast-fed, with no use of infant formula.
- Mixed-fed, i.e., Breast-feeding combined with use of formula.
- Formula-fed, i.e., Use of formula only, with no breast-feeding.

Iodine concentrations were measured in maternal breast milk, mother and infant urine samples, and maternal dietary intake from an iodine-specific food-frequency questionnaire [FFQ]. Infant dietary intake of iodine was assessed by questionnaire completed by the mother. In addition, blood samples were taken from the infants at 3 and 6-months to measure thyroid hormone status.

The aim of the study was to investigate the associations between infant urinary iodine concentrations and predictors of maternal iodine status, i.e., breast milk iodine concentration and feeding method. The study also aimed to investigate the associations between maternal iodine status and infant thyroid function.

For context, the WHO threshold for urinary iodine sufficiency in infants is 100mcg/L [(1)], and for breastmilk iodine concentration ≥92mcg/L is required to meet infant requirements [(8)].

Results: 113 infants were followed-up over the 3, 6, and 11-month postpartum visits. Mean age of the mothers was 29-years, and the average gestational week at birth was 40. At 3-months, 80% of infants were breast-fed exclusively, 15% mixed-fed, and 5% formula-fed. At 6 and 11-months, the proportion of infants' breast fed was 78% and 58%, respectively.

***Associations Between Infant Iodine Status and Maternal Iodine Status*:** At 3-months postpartum the average infant urinary iodine concentration was 82mcg/L, which increased to an average of 110mcg/L at 6 and 11-months, respectively. Overall, 61% of infants were under the WHO threshold of 100mcg/L at 3-months, which declined to 41% and 37% at 6 and 11-months, respectively.

The average maternal breastmilk iodine concentration at 3-months postpartum was 77mcg/L. Infant urinary iodine concentrations positively correlated with maternal breast milk iodine with a moderate strength of correlation.

Maternal urinary iodine concentrations and dietary iodine intake assessed through the FFQ also positively correlated with infant urinary iodine status, with similar but slightly weaker strengths of correlation.

***Associations Between Infant Iodine Status and Breastfeeding Status*:** At 3-months postpartum the average infant urinary iodine concentration was 76mcg/L in breast-fed infants compared to 190mcg/L in formula-fed infants.

At 6-months the difference was 105mcg/L and 315mcg/L in breast-fed and formula-fed infants, respectively. At 11-months postpartum there were no differences in infant iodine status between either breast-fed, mixed-fed, or formula-fed infants.

***Associations with Infant Thyroid Hormones*:** No infants had T4 levels outside of references ranges, and no infants were classified as overt hypo or hyperthyroid. Neither infant urinary iodine concentrations nor maternal breast milk iodine concentrations were associated with infant thyroid status.

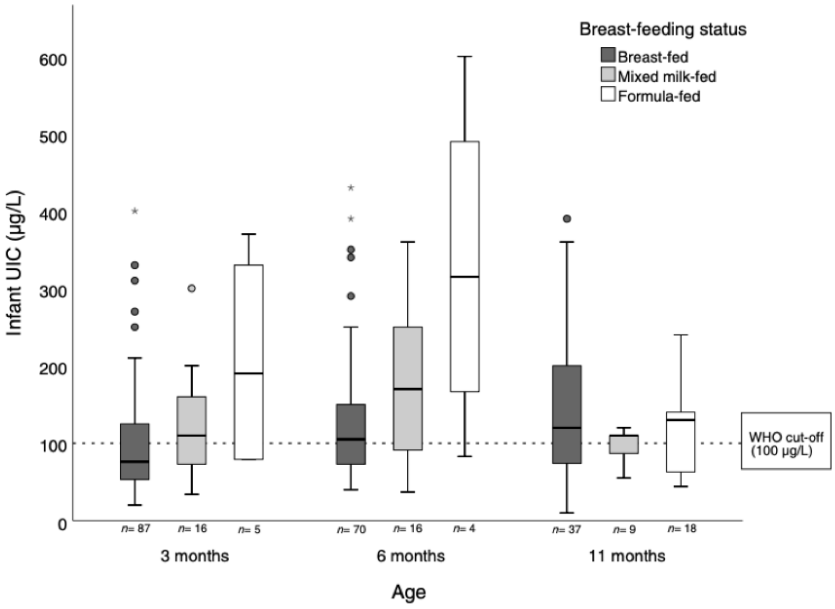

***Figure** from the paper illustrating infant urinary iodine concentrations at each follow-up visit, according to feeding status. Dark grey bars indicate breast-fed infants, light grey indicate mixed-fed, and white bars indicate formula-fed infants. The WHO threshold for sufficiency of measured infant urinary iodine concentrations of 100mcg/L is indicated by the dotted line from the left Y-axis.*

The Critical Breakdown

Pros: The parent RCT was preregistered. The aims of the present study were clearly stated. The study used multiple methods of assessing maternal iodine status, including breastmilk, urinary samples, and dietary assessment [discussed further under ***Key Characteristic***, below]. The study also included assessments of infant iodine and thyroid hormone status at multiple timepoints over the first year of life. Only 5% of the infants were born before gestational week 37, so the overall cohort is not likely confounded by early term births. The main strength of the study is the assessment of infant iodine status relative to feeding method [discussed further under ***Interesting Finding***, below].

Cons: This is a secondary analysis of an RCT, and as such is an observational study rather than direct test of the influence of maternal iodine intake on infant iodine and thyroid status. There are challenges of research in infants, evident in different levels of missing data from infants at each of the follow-up visits. Breastmilk iodine status was only assessed at 3-month postpartum. The lack of sufficient data on infant thyroid function may mean that the analysis was underpowered to detect associations. The categorisations of feeding status meant that there were few infants in the mixed-fed and formula-fed groups, which may have influenced the estimates and magnitudes of differences in iodine status observed. The women were only recruited around week 18 gestation, and thus there is a lack of data on iodine status in the first trimester. The sample size is modest, and consists of young women from Norway, which may not generalise to other populations with differing iodine statuses.

Key Characteristic

The study employed a comprehensive assessment of maternal iodine status, which crucially included an assessment of breast-milk iodine concentrations. Generally, urinary iodine concentrations are considered the best biomarker of iodine intake because ~90% of iodine that is ingested through diet or supplements is excreted in urine [(2)].

However, during lactation urinary iodine becomes a less accurate biomarker of iodine intake because the average levels of iodine in urine are lower [(1)]. The reason for this is that during lactation there is greater partitioning of iodine into breast milk [(9)]. Consequently, breast milk iodine concentrations are a more reliable assessment of iodine status in lactating women than urinary iodine concentrations [(9)].

This may also vary relative to iodine status, i.e., in women with inadequate iodine intake the evidence suggests that the body maintains iodine concentrations in breastmilk to ensure adequate provision of iodine to the feeding infant [(9)]. Thus, the assessment of breastmilk iodine status provided a more reliable assessment of maternal iodine status in the present study, and also provided crucial insight into the primary, and most interesting, finding of the study...

Interesting Finding

The most interesting outcome was the differences in infant urinary iodine concentrations relative to feeding status over the first year of life. While we must acknowledge the limitation that there were few infants in the mixed-fed and formula-fed categories at 3 and 6-months, respectively, which may limit the comparisons, ~80% of infants were exclusively breast-fed at these time points.

The fact that these infants were exclusively breastfed is instructive given their relatively iodine insufficiency. It should be noted that iodine sufficiency in infants assessed through urinary iodine levels is debated. While the WHO threshold classifies deficiency as <100mcg/L, a tightly controlled iodine balance study in 2016 suggested that <125mcg/L may better represent deficiency in infants [(8)]. Given that average infant urinary iodine concentrations at 6 and 11-months was 110mcg/L, it could be that even these levels are insufficient depending on the cut-off value used.

What adds interest to this finding is the exclusive breast-fed status of the infants with insufficient urinary iodine concentrations, because this directly reflects inadequate maternal iodine intakes. We know from the parent RCT that the mothers in this study exhibited mild-to-moderate iodine deficiency [10], and from the present study that their breastmilk iodine concentrations were low.

Taken together, these data indicate the importance of achieving sufficient maternal iodine intake, recalling that requirements are double the general adult recommendations, particularly for iodine adequacy in exclusively breast-fed infants.

Relevance

There remain open questions in this area of research, specifically in relation to the optimal threshold for sufficiency in infants using urinary iodine concentrations as a marker, and for breastmilk iodine concentrations in lactating women [8,9]. Nevertheless, even within the parameters of that debate, the mothers in the present study were unequivocally iodine deficient. The infants were deficient at 3-months and depending on criteria applied either remained deficient at 6 and 11-months or were just over the threshold for sufficiency.

The main relevance of the present study is that for exclusively breast-fed infants, maternal iodine intake is the primary factor influencing infant iodine status. Less than half of the women in the present study began supplementing iodine during pregnancy [10], and clearly dietary iodine was inadequate based on both average urinary iodine excretion in the mothers [~100mcg/L] and average breastmilk iodine concentrations [~77mcg/L].

However, these iodine concentrations would be considered in the mild-to-moderate deficiency range, and the evidence for potential adverse effects of mild-to-moderate iodine deficiency is far less consistent [11] than that for severe deficiency [≤50mcg/L] [2]. In addition, most evidence suggests any potential adverse effects of iodine deficiency relate to first trimester iodine deficiency [12], for which we lack data in the present study.

It is important to note that infant thyroid levels appeared to be unaffected by maternal iodine deficiency in the present study. This finding may be limited by missing data on thyroid hormones from the infants, however, it is consistent with previous research that suggests that foetal thyroid production provides mechanisms to protect the foetus from moderate iodine deficiency [13]. For example, there is evidence that children born to mothers with low T4 at term have higher T4 levels than the mother [13].

The overall evidence for iodine in pregnancy and related outcomes in infants suggest that the critical period is early gestation, however, the degree of iodine deficiency may be of greater relevance [11–13]. Of course, both factors may interact to influence the developmental status of infants, and adequate pre-conception iodine remains a valid public health goal.

Application to Practice

Iodine sufficiency in the population appears to relate directly to whether public health policies of iodising salt are in place. For example, in the Americas ~87% of households use iodised salt and this region exhibits the lowest levels of deficiency, while Europe exhibits the highest levels of iodine deficiency and has the lowest coverage of iodises salt [2]. It is also important to note that infant formulas do contain adequate iodine levels, and the data from the present study indicates that this provided more than sufficient iodine status to the infants.

However, where the population level of iodine is in the mild-to-moderate range, this is where the open questions regarding benefits to supplementation remain [11]. Supplementation may be necessary; the parent RCT intervention targeted increasing iodine status with iodine-rich foods, namely cod consumed twice per week, and failed to significantly increase iodine status in the women.

It is possible to achieve iodine adequacy through a combination of supplements [as potassium iodide] and dietary intake, and note that the pregnancy and lactation recommendations are for ~200-250mcg/d total intake.

However, the most important consideration may be timing, as the evidence for adverse effects of maternal iodine deficiency on infant cognitive development relate specifically to first trimester deficiency [12]. Thus, achieving adequate maternal iodine intakes pre-conception appears to be the goal.

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