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Iodine supplements for mildly iodine-deficient pregnant women: are they worthwhile?

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Pregnancy sharply increases the requirement for iodine. This is mainly due to an increase in maternal thyroxine production to maintain euthyroidism and transfer thyroid hormone to the fetus, and an increase in renal iodine clearance (1). The WHO recommends an iodine intake of 250 μg/d for pregnant women, compared with 150 μg/d for nonpregnant women (1). Thus, pregnant women are particularly vulnerable to iodine deficiency (ID) when dietary iodine supply is low.

The first priority of iodine programs is to prevent ID in pregnant women, because ID in utero can cause irreversible brain damage. The WHO suggests a median (m) urinary iodine concentration (UIC) <150 μg/L in a population of pregnant women indicates ID (1). Severe ID (an mUIC in pregnant women of <50 μg/L) is associated with maternal hypothyroidism and decreased intelligence quotient (IQ) in the offspring (2). Whether mild to moderate maternal ID (an mUIC of 50–149 μg/L) increases risk of maternal thyroid disorders or low IQ in the offspring is unclear.

In many countries, iodized salt programs provide adequate iodine to cover the increased needs of pregnancy. When iodized salt is not widely consumed, as in the USA, use of oral iodine supplements could increase iodine intakes during pregnancy (3). However, experts are divided on the need for iodine supplements in pregnant women with mild ID. Whilst acknowledging the lack of data, the American Thyroid Association recommends most women take an iodine supplement during pregnancy (3). In contrast, the WHO does not recommend maternal iodine supplements in countries where iodized salt programs are providing adequate iodine to the general population (1).

Thus, the systematic review by Dineva et al. (4) reported in this issue of the *American Journal of Clinical Nutrition* is timely and relevant. The authors examined the effects of iodine supplementation in pregnant women with mild to moderate ID (defined as a baseline mUIC of 50–149 μg/L) on maternal thyroid disorders and offspring development. In their review, the authors included 37 publications: 10 randomized controlled trials (RCTs), 4 non-RCT interventions, and 23 observational studies. Nearly all studies showed no significant effect of supplementation on maternal or infant thyroid hormone concentrations. However, only 3 RCTs addressed child development and only 1 was adequately powered. Meta-analyses of 2 of these RCTs showed no significant effect on child cognitive, language, or motor scores. The authors concluded there is insufficient good-quality evidence to support recommendations for iodine supplementation in pregnancy in areas of mild to moderate deficiency.

As highlighted by Dineva et al. (4), the best evidence to date comes from an RCT in which pregnant women in India and Thailand were randomly assigned to receive daily 200 μg oral iodine or placebo until term. Women (n = 832) entered the trial at a mean gestational age of 10.7 wk; their mUIC was 131 μg/L. Mean compliance with supplementation was 87%. Iodine supplementation had no significant effect on child neurodevelopment measured at 5.5 y, and no significant effect on maternal or infant thyroid functions (5). Limitations of this study include that the baseline mUIC indicated only mild ID, and many women began supplementation only at the end of the first trimester. It is possible that beginning supplementation earlier would have resulted in different findings, as the fetal brain rapidly develops in the first trimester (2). However, in the trial, there were no significant modifying effects of baseline mUIC or gestational age at entry on the developmental outcomes (5).

It is important to remember that brain damage occurring in utero during ID is not directly caused by a lack of iodine, but indirectly due to inadequate synthesis of thyroid hormones by the mother and the fetus (2). Thus, maternal and/or infant hypothyroidism is likely the best available surrogate marker of risk of cognitive damage (2). Notably, in the review of Dineva et al. (4), despite 7 of the RCTs reporting very low baseline maternal mUICs (<65 μg/L), there was no consistent benefit of iodine supplements on maternal or infant thyroid function. Cross-sectional data suggest risk of maternal hypothyroidism increases only when urinary iodine excretion is below 50 μg/g creatinine (6).

If the potential benefits of iodine supplements are mediated through improved maternal thyroid function, what is the evidence that mild maternal hypothyroidism is detrimental to the offspring

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and its correction is beneficial? Two large RCTs, 1 done in a presumably iodine-sufficient population (7) and 1 in a population with ID (8) failed to show benefits on child development in mothers treated with levothyroxine for mild maternal hypothyroidism. In the latter study, pregnant British and Italian women with mild thyroid dysfunction in early pregnancy were randomly assigned to receive levothyroxine at a starting dose of 150 μg. The pregnant women studied were iodine deficient with an mUIC of ≈ 70 μg/L (9). Although this study did not directly assess the effects of iodine supplementation, ∼100 μg of the daily dose of 150 μg of levothyroxine consisted of iodine, which is released during metabolism of levothyroxine and enters the body iodine pool. Moreover, any impairments of maternal thyroid function caused by ID in the women would have been resolved in the treatment group by levothyroxine. Despite this, levothyroxine supplementation did not improve cognitive function in the children (8).

Proponents of iodine supplements for pregnant women with mild ID argue that most of the available observational data show inverse correlations between maternal iodine intake during pregnancy and offspring development (3). However, confounding is common in observational trials. For example, a first analysis of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in the UK found significant inverse associations between low maternal iodine status (defined as UI/creatinine <150 μg/g) and child verbal IQ at age 8 y (10). However, in a subsequent analysis of the ALSPAC cohort including more women (2980 versus 958 in the original analysis) and adjusting for a more stringent selection of variables, this association was no longer significant (11). A meta-analysis of European birth cohorts that included 6180 mother-child pairs with measures of UIC during pregnancy and child IQ found no significant associations between low maternal iodine status (defined as UI/creatinine <150 μg/g) and child verbal or nonverbal IQ. Moreover, maternal UI/creatinine was not associated with maternal thyroid hormone concentrations (11).

Thus, the available evidence suggests pregnant women may be able to physiologically adapt to mildly low iodine intakes during pregnancy, draw from intrathyroidal iodine stores, and maintain fetal euthyroidism allowing for normal in utero development (1). However, as emphasized by Dineva et al. (4), adequately powered RCTs of iodine supplementation in pregnant women on child development are needed to finally answer this question, and should be a priority of future research in this field.

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