////Title: Iodine Nutrition in Pregnancy and Breast Feeding to Prevent Iodine Deficiency Disorders

////Stand-first: Severe iodine deficiency disorders (IDDs) caused by lack of iodine during pregnancy and early life can result in irreversible brain damage but are avoidable. Professor Creswell Eastman at the University of Sydney in Australia and his colleagues Professors Mu Li and Gary Ma have contributed significantly to the prevention of IDDs arising from severe iodine deficiency in the developing world and is now concentrating on the effects of mild to moderate iodine deficiency globally.

////Body text:

The thyroid gland produces the hormones triiodothyronine (tri-iodo-thi-ro-neen) (T3) and thyroxine (T4). When the thyroid is unable to produce enough hormones or if it isn't stimulated to produce enough hormones due to insufficient thyroid-stimulating hormone (TSH) released by the pituitary gland, this results in hypothyroidism.

From conception to around 20 weeks, foetal brain development is dependent upon thyroxine provided by the mother. During the second half of pregnancy, foetal brain development is dependent upon both mother and foetus thyroxine production. From birth, however, brain development is dependent on the infant's own thyroxine production.

Iodine is essential for thyroid hormone production and a severe lack of iodine during pregnancy can have irreversible, devastating effects on brain development for the foetus. Disorders arising from lack of iodine are termed iodine deficiency disorders (IDDs) and these can result in a wide range of physical, neurological and neurocognitive effects.

Neurological and neurocognitive effects from this irreversible brain damage range from minor or subtle deficits in intelligence and behavioural disorders to congenital hypothyroidism (CH; also known as cretinism). The severity of IDDs depends upon the extent, duration and timing of the iodine deficiency during the pregnancy.

Mandatory universal salt iodisation (USI) is the addition of iodine to all salt to be consumed by humans within a country, including salt used in food processing. USI has largely eradicated severe iodine deficiency globally and focus has now shifted to the effects of less severe deficiency, particularly in the developed world. Professor Creswell Eastman at the University of Sydney in Australia and his colleagues conducted a comprehensive review of studies on IDDs resulting from mild to moderate iodine deficiency.

Thyroxine exists in two forms in the body. Some is free and enters body tissues where needed but most thyroxine is bonded to protein in the blood. A total thyroxine blood test measures both free and bound thyroxine. Measurement of free thyroxine is preferred since free thyroxine is available for use by the body. Some studies have linked mild to moderate iodine deficiency during pregnancy with decreased IQ in children, with one specifically identifying an association between lower free thyroxine levels in mothers and lower IQ in their children. However, more in-depth research is required to investigate if maternal levels of thyroid hormones directly correlate with thyroxine transfer to the foetal brain.

Maternal hypothyroxinaemia (hi-po-thi-roc-see-neem-ia) is a condition where the mother may have a normal TSH level together with a low level of free thyroxine. It has been proposed if the cause of maternal hypothyroxinaemia is mild, rather than severe iodine deficiency, then triiodothyronine secretion replaces thyroxine secretion to conserve iodine. This would maintain normal thyroid gland function in the mother but cause underactive thyroid function and brain damage in the foetus due to its dependence on thyroxine. More research into this possibility is needed, particularly as there are well-documented methodological problems encountered in the measurement of free thyroxine in pregnancy, and international clinical guidelines do not routinely recommend this test in pregnant women.

In addition to lower IQ, children affected by mild to moderate iodine deficiency during pregnancy may potentially suffer from less obvious impairments in behaviour, motor function and hearing. Unfortunately, many studies to date have overlooked these more subtle forms of brain damage.

Iodine levels in an individual are often assessed by measuring a spot or one-off iodine concentration in urine (UIC). The analytical methods used to measure UIC can vary in reliability and accuracy, and in any case, a UIC result may vary considerably from day to day with variations in dietary intake and urine volume. As such, Professor Eastman and his team suggest that a spot UIC is not acceptable for effectively evaluating iodine nutritional status in pregnancy.

Neonatal thyroid stimulating hormone (nTSH) concentration is used to detect CH – the heel prick test in newborns. A study of a group of individuals who share a common characteristic, such as age, sex, or health condition is called a population study. Iodine deficiency assessment for a country uses median urinary iodine concentration in school-age children in the population. There has also been a large body of literature using nTSH results to assess iodine deficiency status or outcomes of iodine supplementation programs for the entire country. However, many factors such as smoking, birth weight, mode of delivery and even seasonal variations can influence nTSH results.

In addition to USI, individual iodine supplements can be used to prevent IDDs. To prevent foetal brain damage, the evidence indicates that supplementation is most effective – and possibly only effective – if it begins prior to conception or in the first trimester and is continued throughout pregnancy.

Professor Eastman and his team have shown that with usual dietary iodine levels, a daily iodine supplement of 100 to 150 µg achieves the optimal recommended daily intake of 250 µg for pregnant Australian women. The team points out that this recommendation applies only to pregnant women in Australia as pre-pregnancy iodine intakes may vary considerably elsewhere. Furthermore, not all countries advocate salt iodisation.

Sufficient iodine intake during infancy is also important to prevent postnatal hypothyroidism although it cannot reverse neurological damage from lack of thyroxine that has occurred during pregnancy. Breastfeeding infants receive iodine from breast milk and, the World Health Organization (WHO) recommend a daily dose of 250 µg as potassium iodide for breastfeeding women.

The effects of a severe lack of iodine are well documented but there is conflict in the literature regarding potential harm to mother and baby when iodine intake exceeds requirements. Professor Eastman and his team did not find any convincing studies defining safe upper limits of iodine intake during pregnancy and lactation, though WHO has recommended a safe daily upper limit of 500 µg iodine during pregnancy.

In the developing world where moderate to severe iodine deficiency is prevalent, WHO recommends large 'one off' iodised oil supplements to pregnant women if daily iodine supplementation is impractical. Concerns were raised that excessive iodine intake from iodised oil early in pregnancy may suppress maternal thyroid hormone secretion, and if administered later in pregnancy could have a similar effect on the developing foetal thyroid gland. However, WHO concluded from the available evidence that iodised oil has no harmful side effects and is beneficial in preventing severe IDDs.

Mild and subtle forms of IDDs from mild to moderate iodine deficiency are global public health problems affecting the developing and the developed world. The team concluded that although there is an abundance of research published on the effects of severe iodine deficiency, many unanswered questions remain on the effects of mild to moderate iodine deficiency.

Professor Eastman and his colleagues make several recommendations for future research to ensure valid comparisons on the effects of iodine deficiency in pregnancy and neurocognitive outcomes in children studies. More precise definitions and measurements of iodine deficiency in pregnancy other than spot UIC, and the methods for measuring iodine levels need to be standardised. Similarly, the processes and procedures for IQ and psychomotor tests should be harmonised. Robust clinical studies are needed to investigate how the neurodevelopmental impairments in foetus and infant are caused by iodine deficiency.

Finally, excess intake of iodine during pregnancy should be avoided and the safety and effectiveness of iodine supplements for mild iodine deficiency in pregnancy need to be established.

This SciPod is a summary of the open access review paper 'Optimal assessment and quantification of iodine nutrition in pregnancy and lactation: laboratory and clinical methods, controversies and future directions' from the journal *Nutrients*. https://doi.org/10.3390/nu11102378

For further information, you can connect with Professor Eastman at creswell.eastman@sydney.edu.au