Review Article

Iodine in pregnancy

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Iodine requirements are increased more than 50% during pregnancy. Iodine deficiency during pregnancy can cause maternal and fetal hypothyroidism and impair neurological development of the fetus. The consequences of iodine deficiency in pregnancy depend upon the timing and severity of the hypothyroidism. Children whose mothers were severely iodine deficient during pregnancy may exhibit cretinism, characterized by profound intellectual impairment, deaf-mutism, and motor rigidity. In iodine-deficient areas, studies have demonstrated that iodine supplementation before or during early pregnancy, increases birth weight, reduces perinatal and infant mortality rates, decreases incidence of cretinism and increases developmental scores in young children. Mild-to-moderate maternal iodine deficiency can cause thyroid dysfunction, but whether it impairs cognitive or neurological function in the offspring remains uncertain.

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Iodine is an essential nutrient required for the biosynthesis of thyroid hormones, which are responsible for regulating growth, development and metabolism. In areas of severe iodine deficiency, thyroid nodules can be present in as many as 30% of pregnant women. Dietary iodine requirements are increased in pregnant women for various reasons[1]. Maternal thyroid hormone production normally increases by about 50% during gestation, due to human chorionic gonadotropin stimulation of the TSH receptor and because high estrogen levels induce an increase in the sialylation of T4-binding globulin (TBG), leading to reduced hepatic TBG clearance and increased concentrations of circulating TBG. In addition, the peripheral metabolism of thyroid hormone may be increased due to placental deiodination of T4 to the bioinactive reverse T3. By at least wk 10–12 of pregnancy, some maternal iodine stores are transferred to the fetus to allow for hormone production in the fetal thyroid. Finally, the glomerular filtration rate of iodide increases early in pregnancy, increasing renal iodide clearance and decreasing the circulating pool of plasma iodine. To compensate for renal iodine losses, there is an increased rate of uptake of iodine into the thyroid gland in pregnant women. Maternal and fetal thyroid hormones are essential in regulating the development of the fetal brain and nervous system. Some of these events begin in the second month of gestation, so may be influenced by iodine status and thyroid hormone production prior to conception[2,3].

National Family Health Survey (NFHS-3) 2005–2006 revealed that only 51% of households in India consume iodized salt. According to a recent Indian study, only 17% of household edible salt samples contained the stipulated iodine content of $15ppm when measured by a titration method[4].

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- **Iodine requirements increased by >50% during pregnancy.**
- **Iodine deficiency during pregnancy can cause maternal and fetal hypothyroidism resulting serious consequences.**
- **Excess iodine exposure during pregnancy can also result fetal hypothyroidism.**
- **Dietary supplements >500 µg /day should be avoided during pregnancy.**

Effects of Iodine Repletion During Pregnancy on Neuro-psychological Outcomes in Offspring :

Severe Iodine deficiency in pregnancy has been associated with maternal and fetal goitre and hypothyroidism, increased pregnancy loss and infant mortality, neurodevelopment defects in infant[5]. Findings of observational studies in mild to moderately iodine deficient pregnant women have shown an association of low iodine status of pregnant women with lower IQ, reading ability, and spelling scores in offspring.

In landmark trials of iodine repletion during pregnancy using iodized oil in areas of severe iodine deficiency in Papua New Guinea and Zaire, iodine supplementation was associated with a significant reduction in the prevalence of endemic cretinism and with higher psychomotor development scores in the offspring of iodine treated mothers

Effects of Iodine Repletion during Pregnancy on Birth Weight :

Studies done from Zaire and Algeria have suggested

that treatment with iodized oil during pregnancy result in higher birth weights compared with the birth weights of offspring of untreated mothers.

In an Asian study, household use of iodized salt correlated with increased weight for age and an increased mid-upper-arm circumference

Effects of Iodine Excess :

Excess iodine exposure can also cause serious negative health effects, and can occur through ingestion of supplements, water or foods with high iodine content or via medical treatments or procedures. Acute iodine poisoning may cause gastrointestinal or cardiovascular symptoms, or even coma, after ingestion of many grams of iodine .When iodine is present in great excess, the iodination of thyroglobulin is acutely inhibited via the acute Wolff-Chaikoff effect. After a few days, the thyroid is able to "escape" from the acute Wolff-Chaikoff effect, in part by downregulating NIS on the basolateral membrane and thereby modulating the influx of iodine entering into the thyroid. The fetal thyroid gland does not acquire the capacity to escape from the acute Wolff-Chaikoff effect until approximately 36 weeks gestation. Therefore, a high maternal iodine load could potentially cause fetal hypothyroidism. Sustained iodine intake from diet and dietary supplements exceeding 500 µg daily should be avoided during pregnancy due to concerns about the potential for fetal thyroid dysfunction[4-6].

Definition of Iodine Deficiency in a Population and in Pregnancy :

A median urinary iodine concentration (UIC) in the range of 100–199 µg/l in a population of school-aged children and nonpregnant adults corresponds to adequate iodine nutrition, whereas a median below this specified range indicates that the population is iodine deficient. For pregnant women iodine concentration in the urine should be higher (150– 249 µg/l) to indicate adequate iodine intake. When the median UIC of school-age children is 20 µg/L, a population is considered severely iodine deficient. Breast milk iodine content varies with maternal dietary iodine intake and is lowest in iodine-deficient areas and highest where additional iodine is routinely provided through supplements or universal salt iodization. As long as maternal iodine intake is adequate, breast milk can meet infant iodine needs[7].

When Should Pregnant Women Take Iodine-Containing Supplements ?

The consensus reached by the International Council for Control of Iodine Deficiency disorders (ICCIDD), World Health Organization (WHO), and United Nations Children's Fund (UNICEF) was that pregnant women should not be recommended to take iodine-containing supplements if the population in general is iodine sufficient, with a median UIC ≥ 100 µg/l for at least 2 years.

American Thyroid Association has recommended that pregnant women living in the USA should take iodine-containing supplements, even if the US population is in general iodine sufficient. European Thyroid Association stated in 2014 that a sufficient iodine intake is usually provided by supplementing euthyroid pregnant and lactating women with formulas containing 150 µg iodine/ day, ideally before conception. Both the 2007 and the 2012 Endocrine Society guidelines on thyroid dysfunction in pregnancy stressed the importance of considering the iodine status in the country in general when deciding on iodine supplementation. In severely iodine-deficient regions where salt iodization is infeasible or inadequate, the WHO recommends that oral supplementation, as either a low dose of iodine taken daily or a high dose of iodized oil taken every 6–12 mo, be given to pregnant and lactating women, women of reproductive age, and children under the age of 2 years. The discordance in guidance from different authorities most likely reflects the lack of data to properly indicate when and which dosage of iodine to recommend in pregnancy. Recently a randomised controlled trial done in South East Asia, evaluated cognitive effects on children born after iodine supplementation of pregnant women. The study randomly assigned 832 women from India (n=318) and Thailand (n=514) to receive either 200 µg iodine or placebo once daily until term. The results showed no significant effect of iodine supplementation on neurodevelopment at 5–6 years, including measures of IQ (Wechsler Preschool and Primary Scale of Intelligence) and executive function (Behaviour Rating Inventory of Executive Function). The median urinary iodine concentration of the two cohorts taken together at baseline was 131 µg/L, which was indicative of mild deficiency (threshold for adequacy 150 µg/L).Pregnant women recruited in India were actually iodine sufficient (median 188 µg/L), whereas those recruited in Thailand were iodine deficient (median 112 µg/L)[4]. Therefore, iodine supplementation has doubtful benefit in mildly-to-moderately deficient pregnant women in terms of offspring neurodevelopment (Table 1).

Table 1 — *WHO criteria for the assessment of iodine nutrition in pregnant and lactating women, based on urinary iodine concentrations*

Pregnant Women	Iodine Intake
<150 µg/l	Insufficient
150–249µ g/l	Adequate
250–499 µg/l	More than adequate
≥500 µg/l	Excessive

Recommended Iodine Intakes :

Observational studies have shown associations between both mild maternal iodine deficiency and mild maternal

thyroid hypofunction and decreased child cognition. Iodine supplementation has been shown to improve indexes of maternal thyroid function, even in marginally iodine-deficient areas. However, no data are yet available from randomized controlled trials in regions of mild to moderate iodine insufficiency on the relation between maternal iodine supplementation and neurobehavioral development in the offspring; thus, the long-term benefits and safety of such supplementation are uncertain. The timing of supplementation is likely to be critical because the beneficial effects of iodine on offspring development appeared to be lost if supplementation is started after 10–20 weeks gestation. A cochrane meta-analyses in 2017 has concluded that iodine supplementation in pregnancy decreases the likelihood of postpartum hyperthyroidism and increases the likelihood of the adverse effect of digestive intolerance, in areas of mild to moderate iodine deficiency. Also in the meta-analysis there were no clear effects of iodine supplementation on other important maternal or child outcomes.

Different agencies have recommended different intakes to meet iodine needs of non-pregnant, pregnant and breastfeeding women, ranging from 150 µg to 290 µg a day.

The International Council for Control of Iodine Deficiency disorders (ICCIDD), World Health Organization (WHO), and United Nations Children's Fund (UNICEF) recommended a daily iodine intake of 250 µg for pregnant women and those breastfeeding their babies.

All recommendations suggest 150 µg a day for non-pregnant adult women. The main method of iodine prophylaxis, in pregnancy / women of reproductive age group/ lactating women is universal salt iodization. However if there is not sufficient coverage of the households with iodized salt and in areas of iodine deficiency, additional measures, such as oral supplementation with potassium iodide tablets/ or multivitamins containing iodine, are necessary in pregnant women to provide adequate iodine nutrition.

Iodine can be given as daily oral supplements containing 100–250 µg. Alternatively, iodized oil can be given orally to women of childbearing age, pregnant women and lactating women; usual doses are 200–400 mg iodine/year. In moderately to severely iodine-deficient areas without universal salt iodization, lactating women who receive one dose of 400 mg oral iodized oil after delivery can provide adequate iodine to their infants through breast milk for at least 6 months. Special attention may need to be paid to those with dietary restrictions (eg, lactose intolerant, gluten intolerant, low-carbohydrate, or vegan) because those individuals may have additional needs for iodine supplementation. Women consuming levothyroxine (LT4) regularly do not require supplemental iodine because the substrate is no longer needed for hormone formation (Table 2).

Table 2 — *Recommendations for iodine intake (µg/day) for pregnant and lactating women*

Population	US Institute of Medicine	WHO
Planning Pregnancy	150	
Pregnancy	220	250
Lactation	290	250

Future Research :

Priorities for future research should include

(a) Pre-pregnancy iodine status is a crucial factor in interpreting the effects of iodine supplementation on thyroid function and offspring cognition, and this needs to be taken into account in future trials

(b) the development of new biomarkers of individual iodine status

(c) Controlled trials in mildly to moderately iodine deficient pregnant women, with the primary outcomes being long-term clinical outcomes, such as maternal goiter, postpartum thyroid dysfunction and/or infant development.

(d) Examined the effects of iodine supplementation in lactation in mildly to moderately iodine-deficient regions.

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