University of Glasgow

Brown, C. (2011) Better never to have been believed: Benatar on the harm of existence. Economics and Philosophy, 27 (1). pp. 45-52. ISSN 0266-2671

Copyright © 2011 Cambridge University Press

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

The content must not be changed in any way or reproduced in any format or medium without the formal permission of the copyright holder(s)

When referring to this work, full bibliographic details must be given

http://eprints.gla.ac.uk/78725/

Deposited on: 13 May 2013

Enlighten – Research publications by members of the University of Glasgow
http://eprints.gla.ac.uk

Abstract

Objective: To document iodine status in Indian pregnancies, associations with maternal diet and demographics, and offspring developmental measures.

Design: Longitudinal study following mothers through pregnancy and offsprings up to 24 months.

Setting: Rural healthcare centre (Vadu) and urban antenatal clinic (Pune) in the Maharashtra region of India.

Subjects: Pregnant mothers at 17 (n=132) and 34 weeks (n=151) gestation and their infants from birth to the age of 24 months.

Results: Median urinary iodine concentrations (UIC) were 203µg/L and 211µg/L at 17 and 34 weeks gestation, respectively (range 26-800µg/L). Using the UIC distribution adjusted for within-person variations, extreme UIC quartiles were compared for predictors and outcomes. There was no correlation between urinary iodine concentrations at 17 and 34 weeks, but 24% of those with low UIC in the lowest quartile at 17 weeks had a UIC in the same lowest quartile at 34 weeks. Maternal educational, socio-economic status and milk product consumption (frequency) were different between lowest and highest quartile of UIC at 34 weeks. Selected offspring developmental outcomes differed between lowest and highest UIC quartiles (abdominal circumference at 24 months, and subscapular and triceps skinfolds at 12 and 24 months). However, UIC was only a weak predictor of subscapular skinfold at 12 months and triceps skinfold at 24 months.

Conclusions: Median UIC in this pregnant population suggest adequate dietary provision at both gestational stages studied. Occasional high results found in spot samples may indicate intermittent consumption of iodine-rich foods. Maternal UIC had limited influence on offspring developmental outcome.

Background

Iodine is an essential dietary element, required for the thyroid gland to synthesise thyroxine by iodination of tyrosine. Iodine is present in soil to a variable degree, so found in low amounts in many foods. Dairy and sea-foods are rich sources and supply most human iodine intake[1]. If dietary iodine is insufficient to produce enough thyroxine, blood thyroid stimulating hormone (TSH) rises, and the gland enlarges ('goitre') to compensate. If blood thyroxine (T4) and its active derivative triiodothyronine (T3) fall, many organs fail to function optimally, and classical symptoms of hypothyroidism develop. The impacts of hypothyroidism on pregnancy include spontaneous abortion, still birth, peri-natal death and stunted growth[2].

Depending on severity, iodine deficiency in pregnancy can cause miscarriage, and ultimately infertility. It can cause neonatal hypothyroidism[3], growth failure[4] ,neonatal goitre and neurological impediment[5,6] . Iodine is critical for the maturation of the central nervous system, particularly for myelination. Brain damage increases with the degree of iodine deficiency, the severest consequence being overt cretinism, with severe mental retardation, deaf-mutism, stunting, impaired gait and motor function[7]. In areas of iodine deficiency cretinism may be uncommon, but milder degrees of neurological damage can affect a substantial number, and iodine supplementation improves cognition deficient children[8,9]. Dietary iodine insufficiency is common, in India, with an estimated total of 71 million affected in total[10,11]. Consumption of few dairy products or seafood and large amounts of goitrogen-containing foods may compound this issue[12]. Moreover, the Indian soil may be more iodine-deficient because of high rainfall and flooding, leading to mineral depletion [13]. Iodine deficiency disorders have been tackled in India via the National Iodine Deficiency Disorders Control Programme (NIDDCP)[11,14] but iodine status has seldom been considered in Indian pregnancies[15,16], with studies focussing on defining iodine deficiency in sub-populations[17-19]. Nevertheless, and despite the effort of the NIDDCP, iodine deficiency remains an issue in some regions[38,39]. The prevalence of iodine deficiency may, however, have been overstated due to misunderstanding of the terminology used in the WHO statement[20].

While iodized salt is available in India, with some states having even banned the use of non-iodized salt, salt iodisation (as well as its impact) is still unreliable, in part due to access [20-22]. Indeed, the worldwide National Family Health Survey (NFHS-3) 2005–2006 revealed that

only 51% of households in India consume iodized salt[23]. Furthermore, general health recommendations are to avoid adding salt to foods. Adequately iodized salt contains ≥ 15ppm but according to a recent Indian study, only 17% household edible salt samples contained the stipulated iodine content of >15ppm when measured by a titration method[24].

There is substantial iodine storage, as iodo-tyrosines in the thyroid, so consumption is not required daily. Iodine supplementation or food fortification can normalise TSH[25], reduce endemic goitre, and normalize thyroid metabolism[26,27]. Individual dietary requirements vary: non pregnant adults have a mean requirement of 95µg/day[28]. Goitre, indicating severe deficiency, is found with iodine intakes below 50µg/day[29] . WHO guidelines, classify the severity of iodine deficiency in populations according to median urinary iodine concentrations 100 µg/L, as the lower limit of acceptability for non-pregnant adults[30] . During pregnancy and lactation, requirements are increased. Although T4 is usually converted in tissues to the more active T3, thyroxine itself is required by the developing brain throughout pregnancy[8] . In the first trimester, partial transfer of thyroxine through the placenta to the fetus is essential for fetal neurological development. Later, the fetal thyroid develops sufficiently to produce its own thyroxine, for which extra maternal iodine is still required[31] . Dietary requirement may be increased by increased renal clearance in pregnancy and lactation[32] and dietary iodine intake during pregnancy and lactation have recently been revised by the WHO and ICCIDD to 250 µg/day[30]. Dietary iodine intake is difficult to measure, and urinary iodine (UI) is used as the preferred marker for population iodine status (as approximately 90% of the iodine ingested is excreted), with a lower limit of 150µg/l as a threshold for sufficiency for the pregnant population[30] (**Table 1**).

The present study investigated the iodine status of a pregnant Indian population living in both rural and urban settings, in the Maharashtra region of India, at different stages of pregnancy and the potential for low/marginal maternal iodine status to subtly impair fetal growth and development, without frank hypothyroidism. This may be important because small-for-dates (included in low-birth weight) babies are more likely to develop hypertension, diabetes and related “metabolic syndrome” disorders in adult life[33]. Indian women tend to have small babies[34,35] and Indians are particularly prone to metabolic syndrome[34,36], which has an association with subclinical hypothyroidism[37] and with multinodular goitre in regions with iodine deficiency[38,39].

Study design and methods

This design of this study is longitudinal, with a follow-up of mothers during pregnancy, and follow-up of their infants from birth to 24 months of age (part of a larger IAEA-funded study [40] on determinants of subsequent metabolic syndrome). We recruited 234 healthy pregnant women who agreed to participate during May 2004 to July 2006: 118 pregnant women from a rural primary health care centre at Vadu (~50 km from Pune city) and 116 pregnant women from the antenatal clinic of King Edward Memorial Hospital, Pune, at routine first trimester clinics. Pregnant women were recruited unselected, sequentially, as they attended ante-natal clinics. Women with multiple pregnancy, congenital anomaly of the fetus or a risk factor such as previous Caesarean section, fetal death, neonatal death; preeclampsia, hypothyroidism or a chronic medical condition (diabetes, hypertension, infective illness, etc.) were excluded. Ethical permission for the study was obtained from KEM Hospital Research Centre's ethics committee and all women provided written consent.

Dietary assessment

A trained nutritionist assessed maternal diet at 17 and 34 weeks of pregnancy using a semi-quantitative food frequency questionnaire (FFQ), based on local practices and validated for the Indian population[41], to obtain the frequency of commonly consumed food items. Iodine-rich foods (milk, milk products, seafood including fish and dry fish, and egg) were identified using Indian food composition tables[42]. Milk was either cow's or buffalo's milk. Milk products included ghee, butter, curds, cheese (though cheese is very rarely consumed). Seafood included all types of fish and dry fish. For each food group, daily, weekly or monthly frequency of consumption of individual foods was recalled since the previous visit of the subject. This frequency was summed to give a composite score of frequency of consumption per month. Frequent consumption was defined as equal to or greater than twice a week. Although data was collected for most of the iodine rich food items, the use of iodized salt was not recorded. Data were not available for use of iodine-fortified products.

Maternal measurements

Demographic data including Standard of Living Index (SLI)[23], location (urban or rural) and educational level (in years) were collected at 17 weeks. Gestation was confirmed by

ultrasound measurement at all appointments. Standard anthropometric measurements were made and bioimpedance measurement using MultiScan 5000 (Bodystat Ltd, Isle of Man, UK) following standard procedure[43].

At each visit, fasting blood samples from the antecubital vein were collected in the sitting position, in an EDTA Vacutainer. Haematological measurements were carried out as reported previously[40,41,43].

Fresh fasting urine samples were obtained from 166 of the 234 participants, and were collected into sterile sealed containers, and frozen at -70°C at 17, 28 and 34 weeks gestation (132, 31 and 151 urine samples, respectively). Specifically, samples at both 17 and 34 weeks were collected for 117 participants. The urine samples collected at 28 weeks are not described here, and only included for adjustment purposes (see statistical methods). No dip-stick testing was performed, as it has been shown to affect iodine measurements[44]. Urinary iodine concentration was measured using the simple Microplate Method (Bioclone Urinary Iodine Assay Kit) based on the Sandell-Kolthoff reaction using Victor System (PerkinElmer, Turku, Finland). Coefficient of variation is quoted by the manufacturer as 9.2% for low values and <6% for medium and high values, both inter- and intra-batches. Samples were analysed in duplicate and iodine concentrations were calculated with reference to external standards.

Neonatal measurements

Detailed neonatal anthropometry was conducted at birth. Birth weight (to the nearest 0.001kg, ATCO Pvt. Ltd, Mumbai, India), length (to nearest 0.1 cm, using Pedobaby, ETS J.M.B., Brussels, Belgium) and skinfolds (to the nearest of 2mm using Harpenden's skin calliper, Chasmors Ltd, London, UK) were measured immediately following birth. Follow-up anthropometry and data on breast feeding were collected at 3, 6, 12 and 24 months. Anthropometric measurements were recorded in duplicates by trained observers, using standardized methods. The coefficient of variation between the observers for different measurements was 2%.

Cord blood was collected at birth from the placental end of the cord. The blood was centrifuged at 2500 *g* for 15 min at 4°C within 1 h of collection and plasma was stored at

70°C until further analysis. Cord plasma glucose and insulin were analysed as per the protocol used for maternal measurements. Data on Social Interaction Score of babies were collected at 24 months, as previously described[45].

Statistical methods

Data are presented as mean (SD) or median as appropriate for continuous variables, or count and frequencies for discrete variables. Normality of continuous data was tested with the Shapiro-Wilks test. Urinary iodine concentration data at 17 and 34 weeks were skewed, and median UICs are reported for comparison against WHO criteria (Table 1).

Repeat UIC samples, available for 122 out of 166 participants (n=2 samples for 96 women, n=3 samples for 26 women) were used to generate adjusted distributions accounting for day-to-day (within person) variations[46] following the detailed National Research Council approach[47] as used by Mackerras et al.[48] (with the caveat that these samples were collected in pregnancy at different gestational stages). This enabled the use of (adjusted) UIC quartiles to group cases to investigate impact on maternal and neonatal characteristics.

Comparisons between the lowest and highest quartiles (defined using the adjusted distributions) were made using the Student's t-test and χ^2 test. Multivariate linear regression was carried out with UIC (17 and 34 weeks, quartiles based on adjusted distributions) and maternal characteristics (maternal age, location, socio-economic status (SLI score), educational level, parity, and for infant outcomes only, offspring gender, gestational age and feeding mode) as predictors. Neonatal and maternal parameters which differed significantly between lowest and highest UIC quartiles at 17 and 34 weeks (t-test, threshold $p<0.1$) were selected as outcome measures. Predictors were removed sequentially from the model according to lack of contribution.

Since this study was hypothesis-generating, $p<0.05$ was assumed statistically significant, without adjustment for multiple correlations. Analyses used SPSS 18.0 (SPSS Inc. Chicago, US).

Results

The median urinary iodine values of women at 17 and 34 weeks gestation were 203 and 211 µg/L respectively. Individual values ranged from 26 to 800 µl/L. Distributions of crude (unadjusted) urinary iodine at both 17 and 34 week gestation are shown in **Figure 1**, along

with the corrected distribution obtained by applying the NRC method. There was no correlation between the two UI measurements, either adjusted (p=0.681) or not (p=0.546), indicating that UI varied within individuals substantially through pregnancy. However, 24% of the women who had a UIC in the lowest quartile at 17 weeks had a follow-up measurement in this same lowest quartile at 34 weeks. Meanwhile, 34% of the women who had a UIC in the highest quartile at 17 weeks had a follow-up measurement in this same highest quartile at 34 weeks.

Maternal characteristics and measurements

Maternal characteristics at 17 and 34 weeks are shown in **Tables 2 and 3**. There was no difference in maternal age, location or parity between lowest and highest quartiles at either 17 or 34 weeks. Educational status and socio-economic status (Standard of Living Index - SLI) was however significantly higher for those in the highest UIC quartile at 34 weeks ($p<0.05$).

Maternal measurements carried out during pregnancy (fasted insulin levels, insulin resistance (HOMA-R), fat mass (BIA), Vitamin B_{12} and haematological measures) did not differ between lowest and highest quartiles at either 17 or 34 weeks, except for the mean corpuscular haemoglobin concentration being higher for those with UIC the lowest quartile at 34 weeks (p=0.021).

Diet and urinary iodine

The consumption of milk products was significantly higher for those with UIC in the highest quartile at week 34 (p=0.002, **Table 4**). No other nutritional parameters differed for those who had UIC between lowest and highest quartile.

Entering the four main class of iodine-rich foods monitored (milk, milk products, eggs and fish) in a multiple linear regression model showed that adjusted UIC at 34 weeks was higher by 0.73 µg/L (CI 0.33-1.12) for each extra serving of milk product consumed, after adjusting for SLI and maternal educational status. The R^2 value of this multiple regression model for adjusted UIC was however only 0.13, leaving a large proportion of variance unexplained.

Influence of maternal urinary iodine on neonatal and infant development measurements

Neonatal and infant development measurements are shown in **Table 5** according to maternal UI status at 17 and 34 weeks. Duration of exclusive breastfeeding did not differ between infants whose mothers had UIC in lowest and highest quartiles at either 17 or 34 weeks (6 and 5 months, respectively, p>0.05). Amongst the offspring measures at birth (gestation, placental weight, birth weight, neonatal length, abdomen circumference, mid upper arm circumference subscapular and triceps skinfolds), there were no difference between the lowest and highest quartiles of maternal UIC at either 17 or 34 weeks. There was also no difference between cord plasma glucose and insulin between the two extreme quartiles for maternal UIC.

Similarly, no differences were observed for any of the infant measures at 3 or 6 months, between the lowest and highest quartiles of maternal UIC.

Among infants at age 12 months there were significant differences in the subscapular and triceps skinfolds beween those, born to mothers with UIC in the lowest and highest quartiles at 34 weeks, (both measures p=0.01). These differences were also seen at 24 months (triceps skinfold p=0.02, subscapular skinfold p=0.04). The abdominal circumference of infants at 24 months was significantly different if the maternal UIC at 17 weeks was in the lowest compared to the highest quartile (p=0.03).

Multiple regression analyses

Maternal adjusted UIC at 17 and 34 weeks were entered in multiple linear regression models (alongside maternal age, location, education status, SLI, parity and offspring gender) to predict selected infant outcomes which were significantly different according to maternal iodine status (Table 5). UIC at 17 weeks did not predict abdominal circumference at 24 months (p=0.055). UIC at 34 weeks did not predict triceps skinfold at 12 months (p=0.07), or subscapular skinfold at 24 months (p=0.185). UIC at 34 weeks was however a significant predictor of subscapular skinfold at 12 months (p=0.021, with a decrease of 0.006 cm for every extra µg/L UIC) and triceps skinfold at 24 months (p=0.035, with a decrease of 0.006 cm for every extra µg/L UIC). These regression models accounted for only a very small proportion of the variance observed for each outcome (4% and 3.2%, respectively).

Discussion

Iodine deficiency is one of the WHO nutritional priorities[30]. It is estimated to cause a global loss of 13.5 IQ points at population level[49], constituting the world's greatest single cause of preventable brain damage and mental retardation[50]. Iodine deficiency is still the most widespread cause of maternal hypothyroxinemia in Western societies. Detection at birth, by TSH estimation, is unlikely to identify mild iodine deficiency and would fail to identify those exposed to a period of iodine deficiency earlier in pregnancy, at a time probably too late for the treatment to normalise development. It is therefore possible that many minor learning disabilities may be preventable by advising women to take iodine supplements as soon as pregnancy starts, or earlier if possible[50].

The median urinary iodine values, 203 and 211 µg/L found in the present study at 17 and 34 weeks respectively, lie in the 'adequate' (150-250µg/L) range for pregnant populations, implying that iodine deficiency is unlikely to be a frequent problem in this population[30]. Our results contrast with the study of tribal Indian pregnancies by Menon and Skeaff, who found median UICs of 106 and 71 µg/L at 17 and 34 week of pregnancy, respectively[15]. The difference between the UICs measured in each area of the same country highlights the geographical variation which may be due to cultural / dietary habits, which could include availability of iodine-fortified products and proximity to the sea and access to fish /seafood (Pune is less than 150km / 2 hours drive from the sea, while Ramtek is over 750km / 11hours drive from the sea).

None of the women studied had overt iodine deficiency, with hypothyroidism, either among the 151 from whom samples were available for the present study, or among the 200 women who took part in the complete IAEA survey[40], as hypothyroidism was an exclusion criterion. There was a wide range of individual values, from 26 to 800 µg/L, which cannot be explained completely on the basis of the limited dietary information available. It is possible that some consumed iodine-rich food products intermittently, including iodized salt, but the significant association of urinary iodine with dairy food consumption assessed by the "Milk Product Score" confirms the importance of milk and dairy foods for iodine intake in this Indian population. Iodine is present at about 300-400 µg/L in milk[51] and was shown to sometime occur at higher concentration in indian milk samples (ranging 26-604 µg/L)[52]. Although present in many milk-based foods such as yoghurt and ice-cream, high intake of milk products is unlikely to account for the highest recorded urinary iodine concentration of 800 µg/L (there was no iodine contamination of our samples from dip-stick testing).

A limitation of the present research is its size, small in epidemiological terms, however, the study was conducted in an area believed to include a proportion at possible risk from iodine deficiency, with a sample size on par with other similar studies[15]. The results cannot be regarded as quantitatively definitive, in a sample of 166 pregnant women from two Indian antenatal clinics, but the subjects were unselected and likely to be representative of the region. Moreover, our sample size at each time point should afford us a precision range of ±10% (95% CI)[53]. The distributions of the UIC at 17 and 34 weeks were also corrected for day-to-day (within person) variations using the NRC method relying on repeated spot measurements in the same individuals, as described in a recent review[46] and applied in another cross-sectional survey of iodine status[48], with the caveat that these samples were collected at different gestational time points. This partly addresses the issue associated with small sample size[48] and enabled us to use extreme quartiles to compare the maternal and infant characteristics of our population.

UIC (adjusted or not) at 17 and 34 weeks did not correlate between the two gestational time-points, indicating that iodine status fluctuates and that sustained exposure to toxic or extremely low amounts is unlikely. However, a few women (24%) who had UICs in the lowest quartile at 17 weeks remained in this quartile at the subsequent time point, while 34% of those with UICs in the highest quartile at 17 weeks had UIC in the same highest quartile at 34 weeks. The lowest level we recorded, at 26 µg/L would almost certainly lead to overt hypothyroidism if maintained. Samples were measured as "spot" concentrations, the most reliable indicator of iodine status for a population[54] and would not have been biased downwards, as commonly occurs through having incomplete 24-hour collections. However, spot urine samples are not suitable to establish individual iodine status.

The biochemical and physiological measurements made, to assess growth and both metabolic and social developments were made by highly trained and reliable staff, as part of a IAEA-funded study on determinants of subsequent metabolic syndrome[40]. It has proved possible to conduct medium to long-term follow-up studies on the offspring of carefully characterised pregnancies in this setting. This study adds to a number of other recent papers reporting iodine status in pregnancy[2,16,31,55-57]. The clinical/pathological effects of overt hypothyroidism are insidious, and commonly go undetected. Any adverse effects of mild iodine insufficiency in pregnancy are likely to be very small, and slow to develop. Indeed, the reported impact of maternal UIC on clinical offspring outcomes is weak, and not consistent (as expected in a population which we found out to be iodine sufficient). Our observations suggest that iodine status reflects measures of diet quality, as well as educational

status and social position which could affect growth and development both via poorer diet and by other mechanisms.

This study was not powered to detect associations between maternal iodine status and neonatal or infant developmental outcomes: while some difference in neonatal outcomes identified according to maternal UIC, these outcome measures were not successfully predicted by maternal UIC during pregnancy (alongside other independent variables such as location, gender of offspring, education, feeding mode). Given the frequency of low median urinary iodine figures emerging world-wide in pregnancy (below the WHO cut-off of 150µg/L), without clear evidence for detriment in most cases, there is a need for a large enough study to exclude detriment from subclinical iodine insufficiency, potentially to revise the WHO criterion.

There are many reasons for poor fetal growth, besides low iodine status, which can interfere with thyroid function. Iodine deficiency is more common in younger, and multiparous women, and in smokers. Smoking also impairs fetal growth and can cause goitre, and part of this mechanism is by blocking thyroxine synthesis. Thiocyanate is a goitrogenic metabolite of cyanide found in tobacco (and also in some foods such as cabbage and broccoli, as isothiocyanate)[58,59]. However, smoking, albeit rare among Indian women, can cause competitive inhibition of iodide transport into the cell, causing increased TSH which in turn causes overgrowth of the thyroid gland, producing goitre[58]. None of the women recruited in this study were smokers, and the consumption of goitrogenic foods was not monitored, however these factors need to be considered when exploring the topic of iodine status and thyroid function.

Our data also suggest that women do have occasional consumptions of very high iodine foods, with corresponding occasional high urinary iodine concentrations – up to 800 µg/L. They cannot be fully explained on the basis of the dietary information obtained in this study, and may relate to the (occasional) consumption of food very high in iodine or iodised-foodstuff. There is no report of iodine levels in tap-water for this region. It is possible that these intermittent consumptions (with ample storage in the thyroid) are sufficient to maintain adequate iodine stores, although the usual dietary intakes, and urine concentrations are low. This understanding of iodine and thyroid physiology explains the recent demonstration that, in order to determine the iodine status of individuals, at least ten separate urinary iodine measurements are necessary[53,60]. The fact that dietary iodine need only be consumed intermittently also explains the way in which the WHO/UNICEF recommendations are

formulated[30]. A urinary iodine below 100 µg/L, or 150 µg/L in pregnancy, does not categorise that individual as deficient: instead, an "iodine-deficient population" is considered to be one whose median for the population is below these cut-offs, in which case there are likely to be some individuals with clinical deficiency. Conversely, a population with median urinary iodine above these values is unlikely to contain many individuals who are clinically deficient. Anxiety has arisen from several reports of (high) prevalence of iodine deficiency in the Indian population and elsewhere. However, it appears that several of the prevalence figures in these reports are based on the proportion of individuals with a spot sample UIC below the population cut-off (100 or 150 µg/L), a misinterpretation of the use of the WHO criterion for 'population deficiency'[61]. Statistical methods for the adjustment of the UIC distribution obtained following the collection of repeat spot samples are not frequently reported or used[46,48] and the lack of validation of these methods in specific populations make their use subject to a number of caveats; however, they can be useful to describe sub-groups in cross-sectional studies. The adjustment procedure had very limited impact on the population UIC median (the raw, unadjusted median reported were 203 and 211 ug/L at 17 and 34 weeks, respectively, against 211 and 214 ug/L for the adjusted medians), but allowed the use of quartiles to group cases. Finally, the terminology of the WHO/UNICEF document is confusing: it could be clearer to refer to "population iodine insufficiency", and to reserve the medical term "deficiency" to a clinical diagnosis.

Our study did not monitor TSH during pregnancy since hypothyroid women were excluded from the start; TSH rises with overt iodine deficiency, but possibly too late to warn of insidious cognitive effects[50]. Our data can now provide the basis of a power analysis to help design a definitive study on subclinical iodine insufficiency and the growth and development of offspring. It is possible that small Indian women have lower requirement for iodine than other countries. They may be able to function better, and to be able to provide for pregnancy, on intakes below that which would result in adverse effects in large women. However, many young women need more iodine. Whilst low-level iodine fortification of common foods, or drinks is certainly a valid, and evidence-based, approach (notwithstanding the specific debate about the safety of promoting salt which is fortified with iodide), simple dietary changes could help. Our data confirm the importance of milk and dairy foods as iodine sources, especially when fish is not consumed. Milk is widely available and just 600 mL of milk or yoghurt/day provides the necessary 250 µg iodine. Iodine-rich foods may not need to be consumed daily to provide iodine since it is stored in the body.

References

1. Haldimann M, Alt A, Blanc A *et al.* (2005) Iodine content of food groups. *J Food Compos Anal* **18**, 461-71.
2. Fisher J, Tran T, Biggs B *et al.* (2011) Iodine status in gate pregnancy and psychosocial determinants of iodized salt use in rural northern Viet Nam. *Bull WHO* **89**, 813-20.
3. Kochupillai N, Pandav CS, Godbole MM *et al.* (1986) Iodine deficiency and neonatal-hypothyroidism. *Bull WHO* **64**, 547-51.
4. Blazer S, Moreh-Waterman Y, Miller-Lotan R *et al.* (2003) Maternal hypothyroidism may affect fetal growth and neonatal thyroid function. *Obstet Gynecol* **102**, 232-41.
5. Pop VJ, Brouwers EP, Vader HL *et al.* (2003) Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)* **59**, 282-8.
6. Haddow JE, Palomaki GE, Allan WC *et al.* (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* **341**, 549-55.
7. Delange F (1994) The disorders induced by iodine deficiency. *Thyroid* **4**, 107-28.
8. Patel J, Landers K, Li H *et al.* (2011) Thyroid hormones and fetal neurological development. *J Endocrinol* **209**, 1-8.
9. Melse-Boonstra A, Gowachirapant S, Jaiswal N *et al.* (2012) Iodine supplementation in pregnancy and its effect on child cognition. *J Trace Elem Med Biol* **26**, 134-6.
10. http://www/dnaindia.com/india/report_71-million-hit-by-iodine-deficiency-in-india_1593586. [cited June 2012].
11. Kochupillai N, Mehta M (2008) Iodine deficiency disorders and their prevention in India. *Rev Endocr Metab Disord* **9**, 237-44.
12. Lightowler HJ, Davies GJ (1998) Iodine intake and iodine deficiency in vegans as assessed by the duplicate-portion technique and urinary iodine excretion. *Br J Nutr* **80**, 529-35.
13. Kapil U (2007) Health consequences of iodine deficiency. *Sultan Qaboos Univ Med J* **7**, 267-72.
14. Kumar S (1995) Indicators to monitor progress of National Iodine Deficiency Disorders Control Programme (NIDDCP) and some observations on iodised salt in west Bengal. *Indian J Public Health* **39**, 141-7.

15. Menon KC, Skeaff SA, Thomson CD *et al.* (2011) The Effect of Maternal Iodine Status on Infant Outcomes in an Iodine-Deficient Indian Population. *Thyroid* **21**, 1373-80.

16. Kapil U, Saxena N, Ramachandran S *et al.* (1997) Iodine status of pregnant mothers residing in a district of endemic iodine deficiency in the state of Himachal Pradesh, India. *Asia Pac J Clin Nutr* **6**.

17. Chakraborty I, Chatterjee S, Bhadra D *et al.* (2006) Iodine deficiency disorders among the pregnant women in a rural hospital of West Bengal. *Indian J Med Res* **123**, 825-9.

18. Chakraborty I, Mazumdar P, Chakraborty PS *et al.* (2010) Iodine Deficiency Disorder among Pregnant Women in a Tertiary Care Hospital of Kolkata, India. *Southeast Asian J Trop Med Public Health* **41**, 989-95.

19. Mazumdar A, Jaiswal A, Chatterjee SG *et al.* (2010) Iodine deficiency in pregnancy in a iodine replete area of eastern India. *Endocr J* **57**, S453-S.

20. Kapil U (2011) Presence of Severe Iodine Deficiency in Areas with Adequate Salt Iodization. *Indian J Pediatr* **78**, 1299; author reply -300.

21. Kapil U (2008) Current status of salt iodization and level of iodine nutrient in India. *Afr J Pharm Pharmaco* **2**, 66-76.

22. Kapil U (2000) Status of urinary iodine excretion in post salt iodization phase in selected districts of India. *Indian Pediatr* **37**, 1282-4.

23. International IIfPSIaM. National Family Health Survey (NFHS-3), 2005–2006. Mumbai2007.

24. Bulliyya G, Dwibedi B, Mallick G *et al.* (2008) Determination of iodine nutrition and community knowledge regarding iodine deficiency disorders in selected tribal blocks of Orissa, India. *J Pediatr Endocrinol Metab* **21**, 79-87.

25. Moleti M, Di Bella B, Giorgianni G *et al.* (2011) Maternal thyroid function in different conditions of iodine nutrition in pregnant women exposed to mild-moderate iodine deficiency: an observational study. *Clin Endocrinol (Oxf)* **74**, 762-8.

26. Sooch SS, Deo MG, Karmarka.Mg *et al.* (1973) Prevention of endemic goiter with iodized salt. *Bull WHO* **49**, 307-12.

27. Kochupil.N, Karmarka.Mg, Weightma.D *et al.* (1973) Pituitary-thyroid axis in himalayan endemic goiter. *Lancet* **1**, 1021-4.

28. Zimmermann MB (2009) Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. *Am J Clin Nutr* **89**, 668S-72S.

29. Pettigrew-Porter A, Skeaff S, Gray A *et al.* (2011) Are pregnant women in New Zealand iodine deficient? A cross-sectional survey. *Aust N Z J Obstet Gynaecol* **51**, 464-7.

30. ICCIDD WU. Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers. . Geneva2007.
31. Mian C, Vitaliano P, Pozza D *et al.* (2009) Iodine status in pregnancy: role of dietary habits and geographical origin. *Clin Endocrinol (Oxf)* **70**, 776-80.
32. Delange F (2007) Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodine nutrition. *Public Health Nutr* **10**, 1571-80; discussion 81-3.
33. Barker DJP, Eriksson JG, Forsen T *et al.* (2002) Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol* **31**, 1235-9.
34. Fall CHD, Stein CE, Kumaran K *et al.* (1998) Size at birth, maternal weight, and Type 2 diabetes in South India. *Diabet Med* **15**, 220-7.
35. Margetts BM, Yusof SM, Al Dallal Z *et al.* (2002) Persistence of lower birth weight in second generation South Asian babies born in the United Kingdom. *J Epidemiol Community Health* **56**, 684-7.
36. Misra A, Chowbey P, Makkar BM *et al.* (2009) Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. *The Journal of the Association of Physicians of India* **57**, 163-70.
37. Shantha GPS, Kumar AA, Jeyachandran V *et al.* (2009) Association between primary hypothyroidism and metabolic syndrome and the role of C reactive protein: a cross-sectional study from South India. *Thyroid Res* **2**, 2.
38. Rendina D, De Filippo G, Mossetti G *et al.* (2012) Relationship between metabolic syndrome and multinodular non-toxic goiter in an inpatient population from a geographic area with moderate iodine deficiency. *J Endocrinol Invest* **35**, 407-12.
39. Ayturk S, Gursoy A, Kut A *et al.* (2009) Metabolic syndrome and its components are associated with increased thyroid volume and nodule prevalence in a mild-to-moderate iodine-deficient area. *European Journal of Endocrinology* **161**, 599-605.
40. Katre P, Bhat D, Lubree H *et al.* (2010) Vitamin B-12 and folic acid supplementation and plasma total homocysteine concentrations in pregnant Indian women with low B-12 and high folate status. *Asia Pac J Clin Nutr* **19**, 335-43.
41. Rao S, Yajnik CS, Kanade A *et al.* (2001) Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune maternal nutrition study. *J Nutr* **131**, 1217-24.

42. National Institute of Nutrition. Nutritive value of Indian foods. Hyberabad: Indian council of Medical Research; 1989.
43. Bhat DS, Thuse NV, Lubree HG *et al.* (2009) Increases in Plasma Holotranscobalamin Can Be Used to Assess Vitamin B-12 Absorption in Individuals with Low Plasma Vitamin B-12. *J Nutr* **139**, 2119-23.
44. Chanoine JP, Bourdoux P, Thi NBV *et al.* (1987) Iodine contamination of urine samples by test strips. *Clin Chem* **33**, 1935.
45. Bhate VK, Joshi SM, Ladkat RS *et al.* (2012) Vitamin B12 and folate during pregnancy and offspring motor, mental and social development at 2 years of age. *J Dev Orig Health Dis* **3**, 123-30.
46. Zimmermann MB, Andersson M (2012) Assessment of iodine nutrition in populations: past, present, and future. *Nutr Rev* **70**, 553-70.
47. Subcommittee on Interpretation and Uses of Dietary Reference Intakes, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Appendix E - Adjustment of Observed Intake Data to Estimate the Distribution of Usual Intakes in a Group. Dietary Reference Intakes: Applications in Dietary Planning. Washington, DC: National Academies Press; 2003.
48. Mackerras DEM, Singh GR, Eastman CJ (2011) Iodine status of Aboriginal teenagers in the Darwin region before mandatory iodine fortification of bread. *Med J Aust* **194**, 126-30.
49. Bleichrodt N, Born MP (1994) A metaanalysis of research on iodine and its relationship to cognitive development. *Damaged Brain of Iodine Deficiency: Cognitive - Behavioral - Neuromotor - Educative Aspects*, 195-200.
50. Delange F, Wolff P, Gnat D *et al.* (2001) Iodine deficiency during infancy and early childhood in Belgium: does it pose a risk to brain development? *Eur J Pediatr* **160**, 251-4.
51. McCance RA, Widdowson EM (1951) Composition and function of colostrum and regression milk. *Nature* **167**, 722-.
52. Longvah T, Toteja GS, Upadhyay A (2013) Iodine content in bread, milk and the retention of inherent iodine in commonly used Indian recipes. *Food Chem* **136**, 384-8.
53. Andersen S, Karmisholt J, Pedersen KM *et al.* (2008) Reliability of studies of iodine intake and recommendations for number of samples in groups and in individuals. *Br J Nutr* **99**, 813-8.
54. Andersson M, de Benoist B, Delange F *et al.* (2007) Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr* **10**, 1606-11.

55. Hamrosi MA, Wallace EM, Riley MD (2005) Iodine status in pregnant women living in Melbourne differs by ethnic group. *Asia Pac J Clin Nutr* **14**, 27-31.

56. Saikia TC, Thakur C, Dutta N (1996) Thyroid status of pregnant women in sub-Himalayan iodine deficient Dibrugarh district (North East India). *Ind J Physiol All Sci* **50**.

57. Menon KC, Skeaff SA, Thomson CD *et al.* (2011) Concurrent micronutrient deficiencies are prevalent in nonpregnant rural and tribal women from central India. *Nutrition* **27**, 496-502.

58. Knudsen N, Bulow I, Laurberg P *et al.* (2002) Parity is associated with increased thyroid volume solely among smokers in an area with moderate to mild iodine deficiency. *European Journal of Endocrinology* **146**, 39-43.

59. Laurberg P, Andersen S, Knudsen N *et al.* (2002) Thiocyanate in food and iodine in milk: From domestic animal feeding to improved understanding of cretinism. *Thyroid* **12**, 897-902.

60. Koenig F, Andersson M, Hotz K *et al.* (2011) Ten Repeat Collections for Urinary Iodine from Spot Samples or 24-Hour Samples Are Needed to Reliably Estimate Individual Iodine Status in Women. *J Nutr* **141**, 2049-54.

61. Laurberg P, Andersen S, Bjarnadottir RI *et al.* (2007) Evaluating iodine deficiency in pregnant women and young infants-complex physiology with a risk of misinterpretation. *Public Health Nutr* **10**, 1547-53.

Table 1: Epidemiological criteria for assessing iodine status of the pregnant population based on the median or range in urinary iodine concentrations

Population group	Median urinary iodine concentration (µg/l)	Iodine intake
Pregnant women	< 150	Insufficient
	150 – 249	Adequate
	250 – 499	Above requirements
	≥ 500	Excessive [b]

[b] The term "excessive" means in excess of the amount required to prevent and control iodine deficiency – not necessarily a damaging excess.

554 **Table 2: Characteristics of mothers at 17 and 34 weeks of pregnancy (Maharashtra,**
555 **India, 2004-2006)**
556

	17 weeks (n=132)		34 weeks (n=151)	
Age, y	22.6	(3.7)	-	
Height, cm	154.1	(5.4)	154.2	(5.3)
Weight, kg	47.3	(6.5)	54.5	(7.3)
Education, y	11.2	(3)	11.1	(3.1)
Standard of living index (SLI) Score	37	(8)	36	(8)
Primi-parous	94	(71.2)	106	(70.2)
Multi-parous	38	(28.8)	45	(29.8)
Vegeterian	44	(33.3)	53	(35.1)
Milk (frequently consumed)[#] n (%)	76	(57.6)	83	(55.0)
Milk products (frequently consumed)[#] n (%)	72	(54.5)	91	(60.3)
Fish (frequently consumed)[#] n (%)	11	(8.3)	14	(9.3)
Eggs (frequently consumed)[#] n (%)	20	(15.3)	23	(16.7)
Urinary iodine (raw UIC µg/L)†	203	(752)	211	(774)

557 Values are mean (SD), †median (range)
558 [#]frequently consumed - more than twice a week, Socio-economic status given by Standard of Living
559 Index (SLI) score
560
561

562

563 **Table 3: Maternal characteristics at 17 and 34 weeks according to adjusted UI status**

564 **(Maharashtra, India, 2004-2006)**

565

	17 weeks				34 weeks			
	<25th centile (n=33)		>75th centile (n=33)		<25th centile (n=37)		>75th centile (n=38)	
Age, y	22.4	(3.8)	22.5	(3.6)	22.3	(3.5)	22.9	(3.9)
Height, cm	154.9	(6.4)	154	(5.8)	153	(4.8)	154.3	(5.9)
Weight, kg	46.1	(5.8)	46.6	(6.7)	53.1	(5.4)	54.9	(7.3)
Education, y	10.7	(2.4)	11.6	(2.6)	10.5	(3)	12.0*	(2.9)
Standard of living index (SLI) Score	36.1	(6.9)	36.3	(7.7)	33.3	(8.3)	38.3*	(8.3)
Primi–parous †	21	(46)	25	(54)	25	(50)	25	(50)
Multi –parous †	12	(60)	8	(40)	12	(48)	13	(52)
Urban setting †	15	(50)	15	(50)	14	(42)	19	(58)
Rural setting †	18	(50)	18	(50)	23	(55)	19	(45)

566 Values are mean (SD), or † n (%). *P<0.05, within the same gestation time.

567

Table 4: Average foods frequency consumption per month during pregnancy, at 17 and 34 weeks according to adjusted UI status (Maharashtra, India, 2004-2006)

	17 weeks				34 weeks			
	<25th centile (n=33)		>75th centile (n=33)		<25th centile (n=37)		>75th centile (n=38)	
Milk	12	(15)	21	(23)	13	(17)	13	(3)
Milk products	14	(19)	13	(13)	10	(14)	27*	(29)
Fish	2	(5)	1	(2)	1	(3)	0.5	(1)
Eggs	2	(3)	3	(6)	4	(7)	2	(3)

Values are means (SD) of food frequency consumption per month. *P<0.05, within the same gestation time.

575 **Table 5: Characteristics of offsprings according to maternal UI status (Maharashtra,**

576 **India, 2004-2006)**

	17 weeks					34 weeks				
Size	<25th centile (n=33)		>75th centile (n=33)		p-value	<25th centile (n=37)		>75th centile (n=38)		p-value
At Birth										
Weight (kg)	2.8	(0.4)	2.7	(0.3)	0.23	2.8	(0.4)	2.8	(0.3)	0.95
Length (cm)	48.6	(1.7)	48.3	(1.9)	0.54	48.4	(2.1)	48.9	(1.6)	0.29
Abdominal circ (cm)	29.1	(2)	28.7	(2.4)	0.49	28.6	(2.3)	29.3	(1.8)	0.19
Subscapular skinfold (mm)	4.0	(1.2)	4.1	(0.9)	0.78	4.2	(1.2)	4.2	(0.9)	0.93
Triceps skinfold (mm)	4.4	(1.1)	4.4	(0.7)	1.0	4.6	(1)	4.4	(0.8)	0.52
Cord insulin (mIU/L)	5.9	(5.9)	6.1	(2.6)	0.88	8.0	(5.5)	5.9	(3.7)	0.1
Cord plasma glucose (mg%)	84.3	(28.7)	85.8	(26.4)	0.86	89.6	(28.2)	99	(26.6)	0.18
At 3 months										
Weight (kg)	5.6	(0.8)	5.4	(0.7)	0.32	5.4	(0.7)	5.5	(0.7)	0.68
Length (cm)	61.7	(2.5)	61.1	(2.8)	0.4	60.4	(2.3)	61.0	(2.8)	0.31
Abdominal circ (cm)	39.3	(2.1)	38.3	(2.7)	0.16	38.7	(2.4)	39.3	(2.5)	0.27
Subscapular skinfold (mm)	7.9	(1.8)	7.4	(1.2)	0.29	8.1	(1.5)	7.7	(1.7)	0.29
Triceps skinfold (mm)	8.5	(1.7)	9.1	(1.3)	0.13	9.0	(1.3)	8.9	(1.7)	0.66
At 6 months										
Weight (kg)	6.8	(0.9)	6.8	(0.8)	0.9	6.8	(1)	6.8	(0.7)	0.8
Length (cm)	66.7	(2.8)	67.1	(3.2)	0.62	66.3	(3)	66.7	(3.2)	0.57
Abdominal circ (cm)	41.1	(2.7)	40.7	(2.8)	0.59	40.7	(2.6)	40.8	(2.4)	0.9
Subscapular skinfold (mm)	7.2	(1.7)	6.9	(1.4)	0.57	7.3	(1.8)	6.8	(1.3)	0.25
Triceps skinfold (mm)	8.5	(2)	8.7	(1.9)	0.78	8.7	(1.7)	8.4	(1.9)	0.41
At 12 months										
Weight (kg)	8.2	(1.4)	8.1	(1.1)	0.73	8.2	(1)	8.3	(1)	0.79
Length (cm)	73.7	(4.2)	74.1	(4)	0.73	73.9	(3.6)	74.5	(3)	0.46
Abdominal circ (cm)	43.1	(3.6)	42.4	(2.9)	0.45	43.0	(2.9)	43.0	(3.3)	0.98
Subscapular skinfold (mm)	6.7	(2.2)	6.1	(1.8)	0.29	7.1	(1.9)	6.0	(1.1)	0.01*
Triceps skinfold (mm)	7.8	(2)	7.6	(2.1)	0.75	8.0	(1.2)	7.1	(1.3)	0.01*
At 24 months										
Weight (kg)	10.6	(1.6)	10.2	(1.2)	0.43	10.4	(1)	10.3	(1.2)	0.61
Length (cm)	85.3	(4.4)	84.6	(4.3)	0.6	84.5	(3)	85.4	(3.9)	0.29
Abdominal circ (cm)	46.5	(3.1)	44.7	(2.5)	0.03*	45.5	(2.3)	45.1	(2.6)	0.55
Subscapular skinfold	6.4	(1.4)	5.9	(1.5)	0.21	6.4	(1.4)	5.7	(1.1)	0.04*

(mm)										
Triceps skinfold (mm)	8.3	(1.5)	8.1	(2.3)	0.64	8.7	(1.8)	7.6	(2.1)	0.02*
Social Quotient Score	91	(6)	92	(6)	0.55	92	(5)	92	(6)	0.79
Mental development score	101	(8)	98	(7)	0.16	97	(6)	100	(6)	0.12
Motor development score	113	(5)	111	(4)	0.32	112	(5)	113	(4)	0.2

577

Figure legends

Figure 1: Distributions urinary iodine concentration at (a) 17 weeks of pregnancy, and (b) 34 weeks of pregnancy (Maharashtra, India, 2004-2006). Solid line: crude UICs; dashed lines: UICs corrected for within-person variation.