

Universal salt iodization is successful in Kashmiri population as iodine deficiency no longer exists in pregnant mothers and their neonates: Data from a tertiary care hospital in North India

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ABSTRACT

Introduction: Normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. In pregnancy, the thyroid gland being subjected to physiological stress undergoes several adaptations to maintain sufficient output of thyroid hormones for both mother and fetus. Consequently, pregnant women have been found to be particularly vulnerable to iodine deficiency disorders (IDD), and compromised iodine status during pregnancy has been found to affect the thyroid function and cognition in the neonates. **Objectives:** Two decades after successful universal salt iodization (USI) in the country, there is scarce data on the iodine status of the pregnant women and their neonates. This is more relevant in areas like Kashmir valley part of sub-Himalayan belt, an endemic region for IDD in the past. The objective was to estimate Urinary Iodine status in pregnant women, the most vulnerable population. **Materials and Methods:** We studied thyroid function [free T3 (FT3), T3, free T4 (FT4), T4, thyroid stimulating hormone (TSH)] and urinary iodine excretion (UIE) in the 1st, 2nd, and 3rd trimesters and at early neonatal period in neonates in 81 mother–infant pairs (hypothyroid women on replacement) and compared them with 51 control mother–infant pairs (euthyroid). **Results:** Mean age of cases (29.42 ± 3.56 years) was comparable to that of controls (29.87 ± 3.37 years). The thyroid function evaluation done at baseline revealed the following: FT3 2.92 ± 0.76 versus 3.71 ± 0.54 pg/ml, T3 1.38 ± 0.37 versus 1.70 ± 0.35 ng/dl, FT4 1.22 ± 0.33 versus 1.52 ± 0.21 ng/dl, T4 9.54 ± 2.34 versus 13.55 ± 2.16 µg/dl, and TSH 7.92 ± 2.88 versus 4.14 ± 1.06 µIU/ml in cases versus controls ($P < 0.01$), respectively. The 2nd to 6th day thyroid function of neonates born to case and control mothers revealed T3 of 1.46 ± 0.44 versus 1.48 ± 0.36 ng/dl, T4 of 12.92 ± 2.57 versus 11.76 ± 1.78 µg/dl, and TSH of 3.64 ± 1.92 versus 3.82 ± 1.45 µIU/ml, respectively. **Discussion:** UIE was similar (139.12 ± 20.75 vs. 143.78 ± 17.65 µg/l; $P = 0.8$), but TSH values were higher in cases (7.92 ± 2.88) as compared to controls (4.14 ± 1.06). Although UIE gradually declined from 1st trimester to term, it remained in the sufficient range in both cases and controls. Thyroid function and UIE was similar in both case and control neonates. **Conclusion:** We conclude that pregnant Kashmiri women and their neonates are iodine sufficient, indicating successful salt iodization in the community. Large community-based studies on thyroid function, autoimmunity, malignancies, etc., are needed to see the long-term impact of iodization.

Key words: India, neonates, pregnancy, thyroid function, urinary iodine excretion

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INTRODUCTION

Iodine is required throughout the life cycle, but pregnant women and infants are the populations most at risk of deficiency, because iodine, a substrate for thyroid hormone, is required for normal brain development

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and growth.^[1] Normal pregnancy results in a number of important physiological and hormonal changes as part of adaptation to maintain sufficient output of thyroid hormones for both the mother and fetus.^[2-4] Consequently, pregnant women have been found to be particularly vulnerable to iodine deficiency disorders (IDD).^[5-7] A compromised iodine status during pregnancy has been found to affect the thyroid function of the neonates as well.^[8-10] Pregnant women with normal thyroid stimulating hormone (TSH) levels often have low free T4 (FT4) levels, even in areas in which iodine intake is sufficient within the general population. This condition is termed as hypothyroxinemia and was long considered to be without consequences for the fetus. However, recent findings suggest that hypothyroxinemia can negatively affect child health outcomes, including neonatal behavior and infant cognitive functioning.^[11-13] As it is clear that thyroid hormones are essential for neurodevelopment from early pregnancy onward, data are scarce from populations that have been previously iodine deficient (ID) and have now achieved sufficiency, like in India.^[14-19] There are no reports on the iodine status of the pregnant women and its effect on the neonatal thyroid function from Kashmir valley of North India, part of sub-Himalayan belt, considered to be endemic region for IDD two decades before.^[20] Therefore, we aimed to explore the iodine status of mother–infant pairs in euthyroid and hypothyroid subgroups of Kashmiri pregnant women two decades after salt iodization.

MATERIALS AND METHODS

Subjects

This prospective cohort study was conducted over a period of 2 years, i.e., from September 2009 to September 2011. The pregnant women attending the outpatient departments of endocrinology and gynecology of Sheri-Kashmir Institute of Medical Sciences, Srinagar, were informed about the study. Those who volunteered were made to sign an informed written consent. The study was approved by the ethics committee of our institute as part of a postgraduate thesis protocol. A total of 169 pregnant women in their 1st trimester were enrolled initially in the study. These women were sub-grouped as: (a) hypothyroid pregnant women receiving thyroxine replacement and were designated as cases ($n = 97$) and (b) apparently healthy euthyroid pregnant women were designated as controls ($n = 72$). The exclusion criteria were use of iodine supplements, twin pregnancy, eclampsia, diabetes, history of pregnancy loss, and history of metabolic or genetic disorders in the family for both case and control groups. All cases and controls after enrollment in the study were followed up till delivery and their neonates were followed

up till 1 month of age. The neonates born to these mothers were designated as case neonates and control neonates, respectively.

Methods

Detailed history about any antecedent medical facts was collected from all women, and the necessary clinical examination was done in them, in addition to thyroid gland palpation. Maternal data included parity, co-morbidity, place and mode of delivery, thyroid status prior to pregnancy, and drug intake with dosage at each visit. Maternal thyroid function was determined toward the end of each trimester (approximately a week before or after 12th, 24th, and 36th weeks of gestation) by estimation of total T3 (TT3), total T4 (TT4), free T3 (FT3), FT4, and TSH levels. About 3 ml of venous blood was collected from each subject in each trimester at a predefined time period as determined by their last menstrual period (LMP) in serum vacutainers. The blood was allowed to clot and serum was separated by centrifugation at 2500 rpm and stored at -20°C till processed for various assays. All the subjects were asked to collect spot urine samples for estimation of spot urinary iodine excretion (UIE). The thyroid status of the neonates was estimated between 2nd and 6th days of age.^[21] Again 3 ml of venous blood was collected from dorsal venous arch of hand from each neonate. About 2-3 ml of urine from neonates was bag collected at the time of drawing venous blood sample and immediately stored at -70°C till the estimation of iodine levels.

Assays

All women's and neonates' blood samples were estimated for thyroid function status (FT4, TT4, FT3, TT3, and TSH). FT3, FT4, and TSH were analyzed by electrochemiluminescence assay (Cobas-Roche Elecys 1010 analyzer). The normal ranges of thyroid functions are as follows: T4 (4.5-14.0 $\mu\text{g/dl}$), FT4 (0.7-1.80 ng/dl), T3 (0.60-1.81 ng/dl), FT3 (2.0-4.2 pg/ml), and TSH (0.35-5.5 $\mu\text{IU/ml}$). The intra-assay and inter-assay coefficient of variation (CV) was less than 7% for all three parameters. Iodine excretion was evaluated in casual urine samples that were analyzed for iodine concentration with Sandell–Kolthoff reaction using unique microplate reader. The inter-assay and intra-assay CV were ($<6\%$) within the kit prescribed limits (Bioclone Australia Pty Limited, NSW, Australia). UIE of $<100 \mu\text{g/l}$ was considered as iodine deficiency and $>300 \mu\text{g/l}$ as iodine excess.^[1]

Statistical analysis

SPSS 11.5 version (Chicago, IL, USA) was used to analyze the data. The quantitative variables have been described as

Mean \pm SD. FT3, TT3, FT4, TT4, TSH, and UIE of the cases and controls were compared across all the trimesters and with the FT4, TSH, and UIE of their respective neonates using one-way analysis of variance (ANOVA) followed by Bonferroni correction for pair-wise comparison. FT3, TT3, FT4, TT4, TSH, and UIE of case and control mothers and case and control neonates were compared using Student's "*t*" test for independent samples. A *P* value of <0.05 was taken as significant.

RESULTS

Among the hypothyroid pregnant women receiving thyroxine replacement (cases, $n = 97$), 15 women dropped out at different stages of pregnancy and were excluded from the final analysis, leaving behind 82 case women. Similarly, 21 women dropped out at different stages among the control group women ($n = 72$), leaving behind 51 for the final analysis. A total of 132 neonates born in this study (case neonates = 81 and control neonates = 51) were also analyzed. There was one stillbirth in one of the case neonates. Mean age of cases (29.42 ± 3.56 years) was comparable to that of controls (29.87 ± 3.37 years). Majority of cases were in the age range of 25-30 years (69.5% of cases and 60.8% of controls). The maximum number of subjects was primigravida (40.2% of cases and 58.8% of controls). The deliveries were mostly (98.8%) conducted in hospital among cases, whereas all controls had a hospital delivery, with lower segment cesarean section in 76.8% cases versus 68.6% controls.

Tables 1-3 give comparative description of TT3, FT3, TT4, FT4, TSH, and UIE levels in cases and controls from 1st to 3rd trimester. TT3, FT3, TT4, FT4, and TSH levels in cases and controls were different in the 1st trimester as expected, but UIE was similar (139.12 ± 20.75 vs. 143.78 ± 17.65 $\mu\text{g/l}$; $P = 0.8$). TSH values among cases were higher (7.92 ± 2.88) as compared to controls (4.14 ± 1.06) ($P = 0.03$) as expected, since most of the hypothyroid women were undertreated when pregnant. The difference in TT3, FT3, TT4, and FT4 levels in 2nd trimester was statistically significant, whereas the levels of TT3 and TT4 had statistical significance in 3rd trimester and no difference was noted in TSH levels in either 2nd or 3rd trimester, indicating the effect of thyroxine replacement. The UIE of cases and controls in different trimesters with their respective neonates was similar, but it showed a significant drop with advancement of pregnancy [Figure 1, Tables 4 and 5]. There was significant maternal hypothyroxinemia in cases as compared to controls across all trimesters, indicating under replacement. Table 6 shows the distribution of UIE

Table 1: Comparative description of thyroid function tests and urinary iodine excretion UIE in the 1st trimester among cases and controls

Biochemical parameters	Cases ($n=82$) Mean \pm SD	Controls ($n=51$) Mean \pm SD	<i>P</i> value
T3 (ng/dl)	1.38 \pm 0.37	1.70 \pm 0.35	$<0.0001^*$
FT3 (pg/ml)	2.92 \pm 0.76	3.71 \pm 0.54	$<0.0001^*$
T4 ($\mu\text{g/dl}$)	9.54 \pm 2.34	13.55 \pm 2.16	$<0.0001^*$
FT4 (ng/dl)	1.22 \pm 0.33	1.52 \pm 0.21	$<0.0001^*$
TSH ($\mu\text{IU/ml}$)	7.92 \pm 2.88	4.14 \pm 1.06	0.03*
Urinary iodine excretion ($\mu\text{g/l}$)	139.12 \pm 20.75	143.78 \pm 17.65	0.18

*If *P* value is less than 0.05, then the mean difference is statistically significant, TSH: Thyroid stimulating hormone, FT4: Thyroid stimulating hormone

Table 2: Comparative description of thyroid function tests and urinary iodine excretion in the 2nd trimester among cases and controls

Biochemical parameters	Cases ($n=82$) Mean \pm SD	Controls ($n=51$) Mean \pm SD	<i>P</i> value
T3 (ng/dl)	1.33 \pm 0.32	1.57 \pm 0.18	$<0.0001^*$
FT3 (pg/ml)	2.63 \pm 0.73	3.17 \pm 0.54	$<0.0001^*$
T4 ($\mu\text{g/dl}$)	9.47 \pm 2.37	12.24 \pm 1.88	$<0.0001^*$
FT4 (ng/dl)	1.11 \pm 0.27	1.31 \pm 0.19	$<0.0001^*$
TSH ($\mu\text{IU/ml}$)	5.97 \pm 1.65	4.69 \pm 0.61	0.39
Urinary iodine excretion ($\mu\text{g/l}$)	127.63 \pm 19.43	133.51 \pm 15.36	0.06

*If *P* value is less than 0.05, then the mean difference is statistically significant, TSH: Thyroid stimulating hormone, FT4: Thyroid stimulating hormone

Table 3: Comparative description of thyroid function tests and urinary iodine excretion in the 3rd trimester among cases and controls

Biochemical parameters	Cases ($n=82$) Mean \pm SD	Controls ($n=51$) Mean \pm SD	<i>P</i> value
T3 (ng/dl)	1.27 \pm 0.30	1.45 \pm 0.19	$<0.0001^*$
FT3 (pg/ml)	2.44 \pm 0.61	2.71 \pm 0.48	0.009*
T4 ($\mu\text{g/dl}$)	9.31 \pm 2.18	11.60 \pm 1.88	$<0.0001^*$
FT4 (ng/dl)	1.08 \pm 0.24	1.11 \pm 0.14	0.42
TSH ($\mu\text{IU/ml}$)	4.89 \pm 3.13	5.12 \pm 0.47	0.60
Urinary iodine excretion ($\mu\text{g/l}$)	116.94 \pm 18.25	123.32 \pm 14.81	0.03*

*If *P* value is less than 0.05, then the mean difference is statistically significant, TSH: Thyroid stimulating hormone, FT4: Thyroid stimulating hormone

among cases, controls, and neonates in various categories based on the cut-offs. The UIE of 100-149 $\mu\text{g/l}$ was in the majority of controls (77.77%), whereas UIE of 150-200 $\mu\text{g/l}$ was in majority of neonates (48.48%). None of the subjects had UIE <50 $\mu\text{g/l}$, indicating the iodine sufficiency of our region. The subjects including mothers and neonates from both case and control groups were divided into quartiles of UIE. The lowest quartiles of UIE were 121.7 $\mu\text{g/l}$ and 133.99 $\mu\text{g/l}$ in case and control neonates, whereas the respective highest quartiles were 157.0 $\mu\text{g/l}$ and 157.25 $\mu\text{g/l}$. Similarly, UIE in case and control mothers was 115.4 $\mu\text{g/l}$ and 121.70 $\mu\text{g/l}$ in lower quartile versus 142.10 $\mu\text{g/l}$ and 144.20 $\mu\text{g/l}$ in the

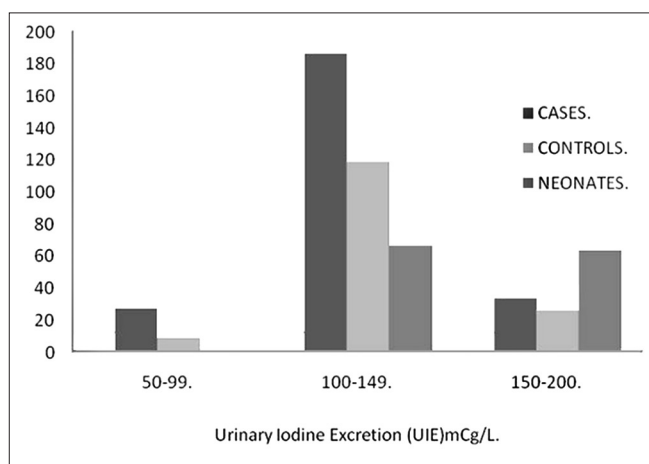


Figure 1: Urinary iodine excretion distribution among cases, controls, and neonates

upper quartile, respectively. The neonates were lesser in weight if born to hypothyroid versus euthyroid mothers (2.54 ± 0.37 vs. 2.79 ± 0.41 kg; $P < 0.05$), but birth length (48.06 ± 1.59 vs. 48.15 ± 1.61 cm), occipito-frontal head circumference (33.90 ± 1.41 vs. 34.26 ± 1.11 cm), and gestational age (36.37 ± 1.45 vs. 36.70 ± 0.70 weeks) were similar in the groups. The incidence of preterm delivery was more in cases (41.46%) as compared to controls (25.49%), as was pregnancy-induced hypertension (30.48% vs. 23.52%). Placental abruption was noted in 14.63% of cases and 5.88% of controls. There was only one stillbirth among case subjects. Iron-deficiency anemia was more frequent in case subjects (56.09%) as compared to controls (25.49%). The incidence of postpartum hemorrhage was also higher in cases (21.95%) against (7.84%) controls.

Table 4: Comparative description of T3, T4, TSH, and UIE of mother–neonate pairs among cases

Biochemical parameters	Cases (n=82)			Neonate (n=81)	P value
	Trimester I (Mean±SD)	Trimester II (Mean±SD)	Trimester III (Mean±SD)		
T3 (ng/dl)	1.38±0.37 ^a	1.34±0.33 ^b	1.28±0.30 ^c	1.46±0.44	a=0.20 b=0.08 c=0.006*
T4 (µg/dl)	9.63±2.33 ^a	9.49±2.38 ^b	9.37±2.17 ^c	12.92±2.57	a=<0.0001* b=<0.0001* c=<0.0001*
TSH (µIU/ml)	6.33±5.8 ^a	4.80±2.74 ^b	4.65±2.07 ^c	3.64±1.92	a=<0.0001* b=0.003* c=0.001*
Urinary iodine excretion (µg/l)	138.70±20.53 ^a	127.23±19.21 ^b	116.50±17.94 ^c	144.62±17.42	a=<0.0001* b=<0.0001* c=<0.0001*

*The mean difference is significant at 0.05 level, TSH: Thyroid stimulating hormone

Table 5: Comparative description of T3, T4, TSH, and UIE of mother–neonate pairs among controls

Biochemical parameters	Control (n=51)			Neonate (n=51)	P value
	Trimester I (Mean±SD)	Trimester II (Mean±SD)	Trimester III (Mean±SD)		
T3 (ng/dl)	1.70±0.35 ^a	1.57±0.18 ^b	1.45±0.19 ^c	1.48±0.36	a=0.003* b=0.09 c=0.64
T4 (µg/dl)	13.55±2.16 ^a	12.24±1.88 ^b	11.60±1.88 ^c	11.76±1.78	a=<0.0001* b=0.18 c=0.64
TSH (µIU/ml)	4.14±1.06 ^a	4.69±0.61 ^b	5.12±0.47 ^c	3.82±1.45	a=0.21 b=<0.0001* c=<0.0001*
Urinary iodine excretion (µg/l)	143.78±17.65 ^a	133.51±15.36 ^b	123.32±14.81 ^c	149.38±11.90	a=0.005* b=<0.0001* c=<0.0001*

*The mean difference is significant at 0.05 level, TSH: Thyroid stimulating hormone

Table 6: Urinary iodine excretion distribution among cases, controls, and neonates

UIE (µg/l)	Cases (n=82×3=246) Cases in 3 trimesters (%)	Controls (n=51×3=153) Controls in 3 trimesters (%)	Neonates (n=81+51=132) Neonates of cases and controls (%)
50–99	27 (10.97)	8 (5.22)	2 (1.51)
100–149	186 (75.60)	119 (77.77)	66 (50)
150–200	33 (13.41)	26 (16.99)	64 (48.48)

UIE: Urinary iodine excretion

DISCUSSION

Iodine is one of the essential nutritional elements in the synthesis of thyroid hormones. The requirement of iodine also increases substantially in various trimesters of pregnancy.^[1] Since iodine is important for synthesis of thyroid hormones which in turn play a major role in the neurodevelopment of fetus from early pregnancy onward, the iodine nutrition of pregnant women has assumed importance especially in endemic areas.^[11,12] The iodine requirements during pregnancy increase since there is an increment in thyroid hormone synthesis to provide for the needs of the fetus, and there is an increased loss of iodine in the urine resulting from an increased renal clearance during pregnancy. UIE is presently the most practical biomarker for assessing iodine nutrition in a population, although not in individuals since it reflects recent iodine intake. Nevertheless, low UI levels probably reflect a prolonged low iodine status in an individual. Three methods have been used to estimate daily iodine requirements in adults: 1) iodine turnover, 2) iodine balance, and 3) UI concentration and thyroid size (1). During early gestation, the fetus depends entirely on maternal thyroid hormones that cross the placenta because the fetal thyroid function does not begin before 12-14 weeks of pregnancy.^[21-23] Even after the onset of fetal thyroid hormone production, the fetus continues to rely upon maternal thyroid hormones.^[22] It is clear that thyroid hormones are essential for neurodevelopment from early pregnancy onwards.^[11,12,22,23] There is little data available from populations which have been ID previously and have achieved iodine sufficiency quite recently.

Many studies conducted in various regions of the world with varying iodine status have assessed the impact of maternal iodine status on that of neonates and also on thyroid function^[3-10,21-23] and neuropsychiatric development of neonates.^[11,12] In studies conducted in Saudi Arabia^[24] and Hong Kong,^[25] maternal free thyroxine and UIE values, respectively, have been found to be negatively correlated with neonatal TSH values. In studies from India, the prevalence of IDD in the pregnant women, as apparent from UIE <10 mg/dl, has been found to be 22.9% and 9.5% in the states of Delhi and Himachal Pradesh, respectively,^[26,27] while few small studies done recently have indicated reasonable iodine sufficiency.^[16-19]

Kashmir valley, located in the sub-Himalayan part of northern India, has been endemic area for iodine deficiency till recently. The universal salt iodization (USI) is in place for more than a decade and there is no

follow-up data to monitor the success of the program. To address this concern, we studied pregnant women and their neonates for urinary iodine status of mother–neonate pairs. To see any effects of iodine nutrition on the current high prevalence of hypothyroidism in pregnant women, we compared hypothyroid women receiving thyroxine with euthyroid pregnant women. TT4 levels were significantly higher in case neonates than in control neonates ($P = 0.006$), which could be reflection of maternal treatment since placenta becomes permeable to T4 toward the term, but TT3, TSH, and UIE of neonates belonging to case and control subjects were similar. Pregnant women with normal TSH levels often have low FT4 levels, even in areas in which iodine intake is sufficient within the general population. This condition, termed as hypothyroxinemia, has long been considered to be without consequences for the fetus.^[1] The UIE of cases and controls in different trimesters with their respective neonates was similar, but showed a significant decline with advancement of pregnancy. The mean TSH values of cases in each trimester were significantly different as compared to controls, as expected. There are many studies which agree with our data and have recorded similar observations.^[22-24] The mean difference for TSH of cases and controls in trimester 1 was statistically significant ($P < 0.03$). The mean difference for UIE of cases across the trimesters as compared with neonates was statistically significant. Pedrerol, *et al.* (2009) studied iodine levels and thyroid hormones in 657 healthy pregnant women. The association between thyroid hormones during the 1st trimester, UIE during the 1st and 3rd trimesters, and birth weight was studied in 557, 251, and 528 mother–newborn pairs, respectively, using linear and logistic regression models adjusted for potential confounders. The median UIE was 95 $\mu\text{g/l}$ and 104 $\mu\text{g/l}$ during the 1st and 3rd trimesters, respectively.^[14] Our population had been ID till two decades back and now seems to be iodine sufficient. None of our cases had suggestion of iodine excess or deficiency. The iodine status of both cases and controls, and their respective neonates suggests the ongoing USI program is successful. Our data also show that the UIE falls as the pregnancy advances, but the fall did not reach the level qualifying iodine deficiency. Similar observations have been made by many authors.^[14-16] Chan-Cua, *et al.* (2003) studied the urinary iodide levels in term newborns and their mothers in Philippines, which included 44 pairs of full-term newborns and their mothers who delivered at two hospitals in Manila. UIE was done during the first 24 h after delivery. Results showed that 18% (8/44) of the neonates were ID (<100 $\mu\text{g/l}$), 71% (31/44) had adequate UIE levels (>100-300 $\mu\text{g/l}$), and 11% (5/44) had high

UIE levels ($>300 \mu\text{g/l}$). None of the mothers had deficient UIE levels. Among the mothers of the neonates who had deficient UIE levels, 50% (4/8) had adequate UI levels and the other half (4/8) had high levels. In conclusion, most term neonates (82%) had adequate to high UIE levels and 18% had deficient UIE levels despite adequate maternal levels.^[15] In contrast to our results, Chakraborty, *et al.*, in a unicentric, hospital-based, non-interventional, cross-sectional study, tried to assess the iodine status of pregnant women attending the antenatal clinic at a medical college in Kolkata, India, during the different trimesters of pregnancy and compared their iodine status with those of age-matched non-pregnant control women. A statistical comparison between the median values for UIE, TSH, FT4, and FT3 in pregnant women and non-pregnant controls revealed a significant difference between the median values for UIE ($P < 0.0047$), TSH ($P < 0.00001$), and FT4 ($P < 0.001$). UIE and FT4 were significantly lower and TSH was significantly higher in pregnant women than in non-pregnant controls. However, no significant difference in median values for FT3 concentration between the groups was seen ($P = 0.4$). Only 4 cases out of 200 pregnant women had an UIE of less than the lower cut-off value for UIE recommended by the WHO corresponding to optimal iodine intake. The results indicated most pregnant subjects did not suffer from significant iodine depletion.^[16] In contrast, Menon, *et al.*, in a prospective, observational study assessing the iodine status of tribal pregnant Indian women living in Ramtek, northeast of Nagpur, showed median UIE of mothers was $106 \mu\text{g/l}$ at 1st trimester, which declined to $71 \mu\text{g/l}$ at gestation (34.5 weeks) and $69 \mu\text{g/l}$ postpartum and that of neonates was $168 \mu\text{g/l}$. 20.0% of women at first visit had TSH $>97.5^{\text{th}}$ percentile and 1.4% had FT4 $<2.5^{\text{th}}$ percentile. Despite three-quarters of the women in this study having access to adequately iodized salt (i.e., $>15 \text{ ppm}$), these pregnant tribal Indian women were ID.^[28] Whether mild to moderate maternal iodine deficiency produces more subtle changes in cognitive function in offspring is unclear; no controlled intervention studies have measured long-term clinical outcomes. Cross-sectional studies have, with a few exceptions, reported impaired intellectual function and motor skills in children from iodine-deficient (ID) areas, but many of these studies were likely confounded by other factors that affect child development. In countries or regions where 90% of households are using iodized salt and the median UI concentration in school-age children is $100 \mu\text{g/l}$, the WHO recommends iodine supplementation in pregnancy and infancy.^[1] The impact of maternal hypothyroidism in neonatal thyroxine and cognitive

development is known. Hypothyroidism is a relatively common illness in pregnancy and about 2.2-2.5% women have been found to have serum TSH levels of 6 mIU/l or greater at 15-18 weeks of gestation.^[1] Very few studies have been conducted on the maternal thyroid function levels during the course of pregnancy in relation to maternal iodine status and there are also limited data from India about the prevalence of thyroid dysfunction in pregnancy. Sahu, *et al.* (2010) conducted a study on overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. They studied 633 pregnant women in 2nd trimester with routine obstetrical investigations and TSH estimation. Significant adverse effects on maternal and fetal outcome were seen emphasizing the importance of routine antenatal thyroid screening.^[13] In the present study, although main outcome measure was to assess iodine status in mother-infants pairs, we observed higher preterm delivery and higher incidence of pregnancy induced hypertension (PIH) and postpartum hemorrhage (PPH). The incidence of borderline TSH ($10\text{-}20 \mu\text{IU/ml}$) was 6.17% ($n = 5$) in case neonates as compared to control neonates 0 (0%). In accordance with our results, LaFranchi, *et al.* (2005) and Montoro (1997) found that untreated hypothyroidism is associated with increased risk for preeclampsia, low birth weight, placental abruption, miscarriage, and perinatal mortality.^[29,30] Maternal iodine supplementation may therefore improve cognitive performance of the offspring, even in areas of mild to moderate iodine deficiency. Several iodine supplementation studies have been performed in mildly ID pregnant women in Europe. These studies have shown that iodine supplementation increases maternal UIE and reduces thyroid volume, as well as prevents increases in infant thyroid volume and thyroglobulin. However, randomized controlled studies with long-term outcomes are lacking. Therefore, two trials were started in 2008 in areas of low iodine status: One in Bangalore, India ($N = 325$), and another in Bangkok, Thailand ($N = 514$). Pregnant women of <14 weeks gestational age were recruited and randomized to either receive a daily dose of $200 \mu\text{g}$ of iodine or an identical placebo throughout pregnancy. Both trials are ongoing, and women are followed up during pregnancy and at delivery. Birth outcomes are recorded, such as gestational age at delivery, height, weight, and APGAR scores, and cord blood and heel stick blood ($<72 \text{ h}$) is collected from the child. Child development is assessed at 6 weeks of age using the Neonatal Behavioral Assessment Scale (NBAS), and at 12 and 24 months of age using the Bayley Scales of Infant Development. The outcomes of these trials will

contribute importantly to the evidence base for iodine supplementation of pregnant women living in areas of mild iodine deficiency.^[13] Similar to our observations, Alvarez, *et al.* showed mean birth weight was less in hypothyroid pregnant women.^[14] We observed no difference in iodine status of euthyroid and hypothyroid pregnant women and their neonates. The data suggest that iodine supplementation through salt iodization program should be continued and monitored strictly with a close surveillance to maintain the normal iodine status in the pregnant women–neonate pairs. The data being tertiary care oriented may, however, have introduced some bias in selection. Community women, especially in rural areas, may differ in their iodine status.

To conclude, this is the first study from Kashmir valley region of India, previously known endemic area of iodine deficiency, demonstrating success of USI at least in pregnant women and their neonates. Although there was no non-pregnant arm, it suggests once the high-risk groups (neonates and pregnant mothers) are iodine sufficient, general population might have achieved iodine sufficiency, although it needs to be studied. Although UIE levels, and serum TT3, TT4, FT3, and FT4 levels showed a steady fall with advancing trimesters in both euthyroid and hypothyroid women on levothyroxine replacement, but at no point during their course of pregnancy did they manifest iodine deficiency. Also, none of the neonates demonstrated iodine deficiency and only two had hypothyroidism (TSH >20 μ IU/ml) needing treatment. The complications observed in hypothyroid pregnant females and their neonates were comparable with other studies.

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