ORIGINAL ARTICLE

Effect of Maternal Iodine Excess during Pregnancy on Neonatal Thyroid Function and Neurodevelopmental Status at 12 Weeks

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Abstract

Objective. This study aims to determine the effect of iodine excess in pregnant mothers on thyroid function, growth and neurodevelopment in the neonates when assessed at 12 weeks of age.

Methodology. This prospective study enrolled term neonates with birth weight >2500 gm of mothers having urine iodine concentration (UIC) ≥500 μg/L documented in the third trimester of the peripartum period. Neonatal TSH was collected by heel prick on dried blood spots within 24-72 hours of age and measured by time-resolved fluroimmunoassay. Neonates with TSH ≥11 mIU/L at birth were followed up at 2 and 12 weeks to monitor thyroid dysfunction, growth and development.

Results. A total of 2354 (n = 1575 in the delivery room) maternal urine samples were collected of which 598 (25.4%) had elevated UIC. Forty-nine (12.2%) neonates had TSH ≥11mIU/L on newborn screening of whom 18 and 3 neonates had residual elevated TSH at 2 and 12 weeks of life, respectively. Maternal iodine levels correlated weakly with TSH at 2 weeks (*rho* = 0.299; *p* = 0.037). No child required treatment for congenital hypothyroidism. Eight babies additionally had TSH >5 mIU/L at 12 weeks of life. The growth and development of babies with or without TSH elevation was comparable at three months (*p* >0.05).

Conclusion. Maternal iodine excess in pregnancy and peripartum period causes transient hyperthyrotropinemia in neonates that did not affect the growth and development at 3 months of age.

Key words: thyroid, hypothyroidism, iodinization, hyperthyrotropinemia, thyroid function test, urine iodine concentration

INTRODUCTION

Iodine is a trace element that is required for the synthesis of thyroid hormones. Optimal iodine nutritional status during pregnancy is required for normal brain development of progeny during fetal and early postnatal life. The prevalence of iodine deficiency decreased after the successful implantation of a universal salt iodization program.[1,2] However, an emerging concern of thyroiditis with iodine excess is instead now being reported India as well as other countries.[3,4]

Iodine excess is implicated in many thyroid-related disorders such as thyroid nodules, hyperthyroidism and hypothyroidism, thyroid neoplasms, thyroiditis and neonatal hyperthyrotropinemia.[5] Fetuses and neonates are at higher risk of excess iodine exposure due to increased permeability of the skin, increase in iodide trapping process and lower renal iodine clearance. Thus, they are unable to escape from the acute Wolff-Chaikoff effect, which blocks the uptake of iodine by the thyroid gland and impairs thyroid hormone synthesis. This process is further accentuated when povidone-iodine is commonly used as a disinfectant in obstetrics.[6]

There is evidence for the role of maternal iodine deficiency and transient hypothyroidism in shaping neurodevelopmental outcomes in babies.[7,8] However, literature is sparse regarding the effect of maternal iodine excess on neonatal thyroid function.[8,9] How these transient thyroid disturbances affect long-term neurodevelopmental outcomes in children largely remain unexplored at present.

Urine iodine estimation from spot samples has been validated for population screening for iodine excess rather than 24-hour timed samples.[10] The cutoffs vary during pregnancy and lactation and are affected by circadian rhythm in normal individuals.[11]

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We aimed to evaluate the effect of excess maternal iodine during pregnancy on neonatal thyroid function, growth and neurocognitive development in affected babies from birth until 12 weeks.

METHODOLOGY

A prospective observational single-centre study was done in a tertiary care setting, Lok Nayak Hospital, Delhi between November 2017- November 2018. The institutional ethics committee duly approved it. Pregnant women attending antenatal clinics in their third trimester were enrolled in the study. Women without regular antenatal checkups, those with previously detected thyroid dysfunction, and those with a history of intake of drugs which affect thyroid metabolism like lithium, amiodarone, and antepartum hemorrhage were excluded. A gestation assessment was done by first-trimester ultrasonography.

After taking informed consent, demographic details, age and associated comorbidities were recorded on a pro forma. A random urine sample (avoided morning sample) of 20 ml was collected from the pregnant women during the third trimester visit in a wide-mouthed screw-capped plastic bottle and was stored at minus 20°C after immediate transport to the laboratory. The visits in the third trimester were either scheduled visits or during active labor for mothers who chose to deliver in the hospital.

A qualitative iodine estimation was performed using the 'wet digestion method' on urine samples within 48 hours to identify those with iodine concentrations ≥500 μg/L. In this method, urine was digested with chloric acid under mild conditions and iodine concentration was determined manually through its catalytic role in the reduction of ceric ammonium sulfate in the presence of arsenious acid. As the reduction proceeded, the intensity of the colour decreased which was measured in a spectrophotometer at 420 nm. This method used for public health purposes is quick, cost-effective, and reported to give results in close agreement with the gold standard techniques such as neuron-activation analysis or inductively coupled plasma mass spectrometry.[12]

Healthy singleton breastfed term neonates (gestation of completed 37 weeks until 42 weeks) with birth weight >2500 gm who were delivered to mothers with UIC ≥500 μg/L were considered eligible for enrolment. Babies born with congenital malformations, birth asphyxia or who required admission to the neonatal intensive care unit were excluded. Socio-demographic details of the mother like age, parity and iodized salt intake were recorded on a predesigned pro forma.

A heel-prick blood sample was taken from the neonates who fulfilled the eligibility criteria as part of routine newborn screening between 24 to 72 hours of life, preferably at discharge, whichever was later. The sample was spotted on filter paper (Whatman 903-grade paper). A circular dried blood spot (DBS) was punched and subjected to measurement of thyroid stimulating hormone (TSH) using solid phase, two-site fluoroimmunometric assay based on direct sandwich technique (Perkin Elmer Life Sciences, Turku Finland). The manufacturer prepared standards and controls with a haematocrit of 50-55% and the reference standard used was WHO 2nd reference international standards. The limit of detection of the assay was 2 μU/L and the coefficient of variation was less than 5%. The blood sample for confirmation of thyroid hormone levels was collected as a venous sample on follow-up. The values of TSH reported on DBS at birth were in whole blood units and at 2 and 12 weeks were in serum units on venous samples (serum units = 2.2 whole blood units).[13]

Babies who had elevated TSH levels (≥44 mIU/L serum units or ≥20 mIU/L on DBS) on the first screen necessitated treatment for congenital hypothyroidism with oral levothyroxine at 10-15 ug/kg per day and were excluded from the study. For the purpose of this study, babies with TSH ≥11 -44 mIU/L of serum units (≥5 – 20 mIU/L on DBS) were considered for confirmatory testing. The DBS was repunched from a different circle for repeat TSH estimation. Those neonates with elevated TSH values (≥11 mIU/L serum units or ≥5 mIU/L whole blood units) on repunch were followed up to evaluate the thyroid function tests (TFT) on venous blood at 2 weeks of life. Any baby fulfilling the criteria for congenital hypothyroidism on confirmatory testing was started on thyroxine as per protocol.[13]

A venous sample for measurement of TSH, fT3 and fT4 was repeated at 12 weeks of life in those neonates with TSH >5 mIU/L. Venous TSH was estimated using the electrochemiluminescence immunoassay (ECLIA) with a normal range of 0.58 – 5.57 mIU/L (serum units); fT4 and fT3 were measured using equilibrium dialysis or ultrafiltration as a reference method for standardization in the Cobas e 620 autoanalyzer with Elecsys fT3 III/ fT4 II assay. The normal range of fT3 was 3.1-6.8 pmol/L with a measuring range 0.4 - 50 pmol/L. Age appropriate cutoffs were used to interpret fT4 levels as 14.5 – 29 pmol/L on day 0-14 and 13.4 – 44 pmol/L at 12 weeks and a measuring range 0.3 - 100 pmol/L.[14] TSH was considered as raised at levels ≥11 mIU/L (more than 10 mIU/L) after two weeks of age.[13] Transient hyperthyrotropinemia was defined as babies with only TSH elevation and transient hypothyroxinemia was when they had associated low fT4.

Babies were followed up at 12 weeks for measurement of weight and length by the same person to minimize inter-observer bias. Weight was measured on a digital weighing scale with minimal clothing measuring 100 grams. Length was measured using standard procedures on an infantometer with a minimum measure of 0.1 cm. Three consecutive readings were obtained and the average of the 3 readings was considered for all the measurements. Anthropometry was interpreted as per WHO growth charts 2005.[15]

The neurocognitive development of these neonates was assessed using DASII (Development Assessment Scale for Indian Infants) at 12 weeks of completed age by a pediatrician who was part of the study team. Two developmental domains, namely motor and mental domains were separately scored. A score of >70 was considered as normal.[16]

The urine iodine of the mothers of the enrolled neonates was also estimated at 12 weeks postpartum for the persistence of increased urinary iodine excretion. Cut-offs for maternal urine iodine concentration (UIC) were adopted from WHO guidelines.[11] In pregnant mothers, iodine insufficiency was considered at UIC <150 μg/L, above requirements at between 250-499 μg/L and excessive at ≥500 ug/L. A UIC level of <100 ug/L was deemed insufficient and ≥100 ug/L was considered adequate during lactation.[11]

Sample size

Considering a prevalence of 34% obtained from a previous study regarding transient hypothyroidism or persistent hyperthyrotropinemia in neonates born to mothers with excessive iodine intake conducted in Japan by Nishiyama et al.,[9] with 5% absolute precision and confidence interval of 95%, the required sample size was 345. We proposed to take a sample size of 400, considering the attrition to be 10%.

Statistical analysis

STATA 11 software was used for statistical analysis. The Kolmogorov–Smirnov test was used to check the normality of data. Thyroid function tests, anthropometric parameters and developmental quotients were expressed as their means and standard deviations/ median (IQR) as per the normality of data. To compare continuous parameters in two groups for parametric or non-parametric data, Student's t-test or Mann-Whitney U test was used. Spearman correlation coefficient (*rho*) was calculated to check the correlation between two continuous nonparametric variables. The missing values were not adjusted or imputed in the final analysis.

RESULTS

A total of 2610 samples were collected from pregnant mothers out of which 2354 urine samples (1575 in the delivery room and 779 during routine antenatal visits) were processed during the study period. Urine iodine level of ≥500 μg/L was observed in 598 (25.4%) pregnant mothers. After applying the exclusion criteria, 494 pregnant mothers were selected for neonatal evaluation with a total of 400 enrolled after excluding neonates who did not meet the eligibility criteria (Figure 1).

The mean (SD) maternal age was 25.1 (7.3) years and the period of gestation was 38.3 (3.6) weeks. A majority of mothers 207 (52%) were multiparous and 289 (72%) had delivered vaginally. Iodized salt was used by 97.5% of the population.
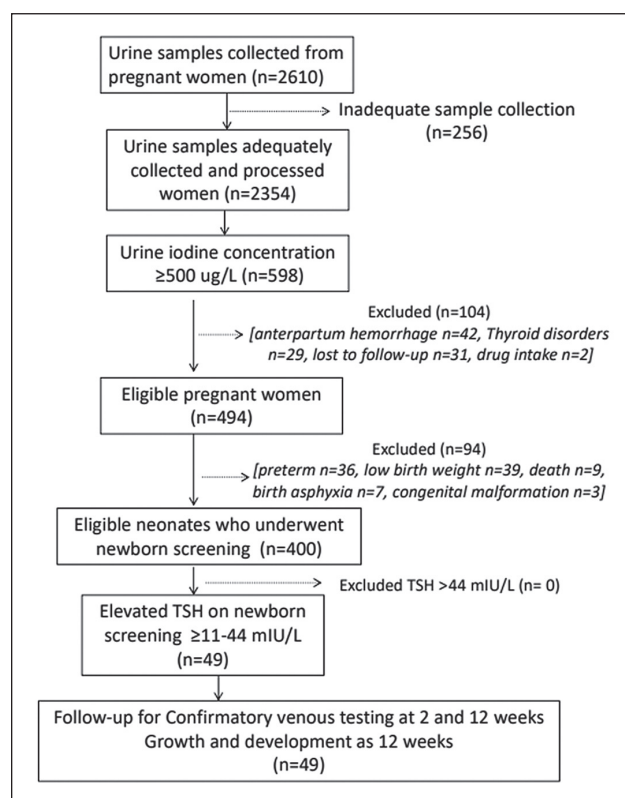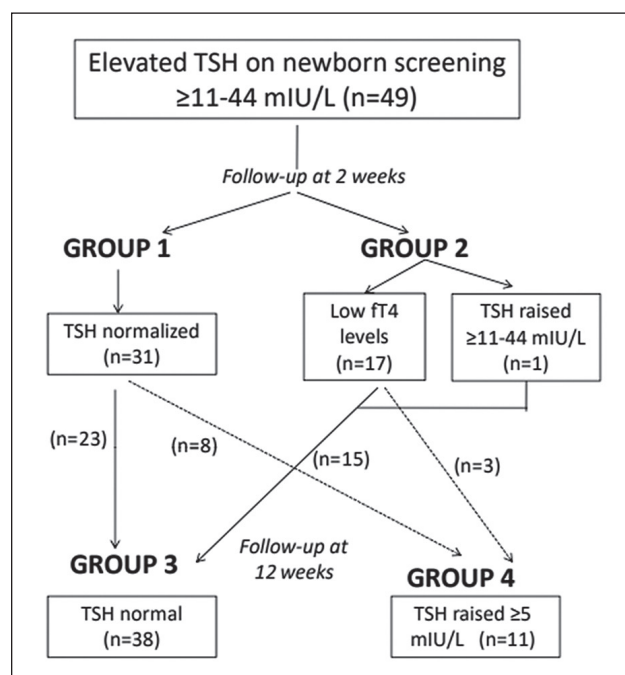

Figure 1. Flow of the study.

**Figure 2.** Study groups as per follow-up at 2 and 12 weeks.

The mean (SD) birth weight of neonates enrolled (n = 400; 209 males) was 2872.8 (530.3) grams. A total of 49 (12.2%, 95% CI 15.44%- 18.99%) neonates had TSH ≥11 mIU/L and were followed up till 12 weeks of age, with all of them breastfed. All babies normalized their TSH levels except one baby with TSH of 25.04 mIU/L at day 14 (fT4 14.1 pmol/L) who tested normal on repeat venous sample at day

28 (TSH 15 mIU/L, fT3 4.5 pmol/L, fT4 18 pmol/L) and did not require thyroxine replacement. Eighteen babies (4.5%, 95% CI 2.47% to 6.53%) had low fT4 levels at two weeks. A comparison of neonates who normalized their TSH (Group 1) and those with low fT4 (Group 2) at two weeks is shown in Table 1.

On follow-up, 15/18 babies in Group 2 had normalized the TSH at 12 weeks of age (Group 3). Three babies from Group 2 and eight babies (originally from Group 1) had TSH ≥11 mIU/L (Group 4); Figure 2. Table 2 compares the biochemical parameters in babies who had normalized thyroid functions (Group 3) and those who had a persistent elevation of TSH with normal fT4 levels (Group 4). No baby had hypothyroxinemia at 12 weeks of age.

The median (IQR) maternal UIC at 12 weeks was 84 (40,100) ug/L. The correlation (*rho*) between maternal UIC at 12 weeks and TSH at birth and 12 weeks was weak (*rho* = 0.156; *p* = 0.285) and (*rho* = 0.191; *p* = 0.189), respectively. The maternal UIC correlated significantly, albeit with a weak direct correlation with infant TSH at 2 weeks (*r* = 0.299; *p* = 0.037); (Figure 3). There was no significant correlation between maternal UIC and fT4 at 12 weeks (*rho* = 0.153; *p* = 0.295) or between DASII scores and thyroid hormone levels at any age (*p* >0.05, data not shown).
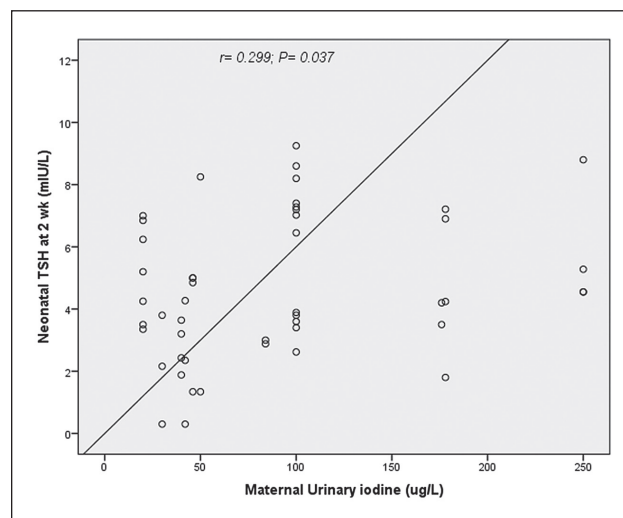
Figure 3. Correlation between maternal urinary iodine concentration and neonatal TSH levels at 2 weeks.

Table 1. Comparison of babies according to thyroid profile at two weeks of life

Parameter	Group 1 (n=31)	Group 2 (n=18)	*P* value
Maternal Age, y	25.4 (3.2)	26.0 (3.7)	0.543
Gestational age, wk	38.6 (1.7)	38.5 (1.2)	0.752
Birth weight, g	2962.4 (538.2)	3017.2 (454.0)	0.718
TSH on DBS[a], mIU/L	7.7 (5.9, 9.8)	9.3 (5.7, 14.9)	0.685
TSH at 2 wk[a], mIU/L	4.6 (3.4, 7.0)	3.8 (2.3, 5.6)	0.175
fT4 at 2 wk, pmol/L	17.8 (2.6)	12.9 (1.8)	<0.001
fT3 at 2 wk, pmol/L	5.1 (1.9)	4.3 (1.3)	0.097
Weight at 12 wk, g	6270.3 (670.2)	5882.3 (659.1)	0.391
Length at 12 wk, cm	60.0 (3.1)	60.0 (2.5)	0.435
TSH at 12 wk[a], mIU/L	3.9 (3.1, 5.2)	3.8 (2.5, 4.9)	0.851
fT4 at 12 wk, pmol/L	16.9 (3.3)	16.2 (2.1)	0.435
fT3 at 12 wk, pmol/L	5.5 (1.6)	4.9 (0.9)	0.211
DASII, mental score	100.9 (7.1)	107.2 (9.1)	0.07
DASII, motor score	100.1 (6.4)	101.9 (6.3)	0.353
Maternal UIC at 12 wk[a], ug/L	100.1 (40.0, 176.0)	46.0 (37.5, 100)	0.247

Data expressed as mean (SD) or [a]median (IQR); Group 1: Babies with raised TSH levels and normal fT4; Group 2: Raised TSH with low fT4; TSH on DBS in whole blood units, TSH on 2 and 12 weeks in serum units; DASII Developmental Assessment Scale for Indian Infants; UIC Urinary iodine concentration at three months post-partum; Comparison by t-test or [a]Mann Whitney U test; P value <0.05 as significant

Table 2. Comparison of babies according to thyroid profile at 12 weeks of life

Parameter	Group 3 (n=38)	Group 4 (n=11)	*P* value
Maternal Age, y	25.6 (3.4)	25.5 (3.5)	0.941
Gestational age, wk	38.4 (1.5)	39.2 (1.8)	0.147
Birth weight, g	2947.1 (512.1)	3105.0 (480.1)	0.366
TSH on DBS[a], mIU/L	7.5 (5.8, 10.2)	9.4 (5.9, 12.7)	0.446
TSH at 2 wk[a], mIU/L	4.1 (3.0, 6.6)	5.3 (3.6,8.8)	0.147
fT4 at 2 wk, pmol/L	15.4 (2.9)	17.8 (3.9)	0.283
fT3 at 2 wk, pmol/L	4.7 (1.4)	5.3 (2.5)	0.032
Weight at 12 wk, g	6112.0 (705.2)	6200.5 (642.3)	0.698
Length at 12 wk, cm	60.0 (2.9)	59.9 (3.0)	0.897
TSH at 12 wk[a], mIU/L	3.5 (2.7, 4.2)	7.2 (6.2, 8.1)	<0.001
fT4 at 12 wk, pmol/L	16.3 (2.2)	17.9 (4.6)	0.276
fT3 at 12 wk, pmol/L	5.1 (1.1)	5.8 (2.1)	0.354
DASII, mental score	102.7 (8.9)	105.0 (6.5)	0.426
DASII, motor score	100.8 (6.9)	100.9 (4.2)	0.937
Maternal UIC at 12 wk[a], ug/L	67.0 (40.0, 100.0)	100.0 (40.0, 250.0)	0.817

Data expressed as mean (SD) or [a]median (IQR); Data compared of the same 49 babies as in table 1; Group 3: Babieswith raised TSH levels and normal fT4; Group 4: Raised TSH with low fT4; TSH on DBS in whole blood units, TSH at 2 and 12 weeks in serum units; DASII Developmental Assessment Scale for Indian Infants; UIC Urinary iodine concentration at three months post-partum; Comparison by t-test or [a]Mann Whitney U test; P value <0.05 as significant

DISCUSSION

This study shows the occurrence of transient thyroid dysfunction in a significant proportion of babies born to mothers with high UIC detected during delivery. However, most of the affected babies recovered by three months of age with normal growth and development in a reassuring manner that reiterates the benign nature of transient high maternal UIC.

Iodine is an essential component of thyroid hormones. Both deficiency and excess of iodine are known to cause adverse effects on human health. Recent studies from India and worldwide have demonstrated an increase in the proportion of goiter and autoimmunity in the post-iodization era. Recent studies from different parts of the world have shown a strong association between iodine excess and thyroid autoimmunity manifesting as goiter, subclinical or overt hypothyroidism.[17,18] Earlier studies have reported up to a 10% incidence of subclinical hypothyroidism in babies with maternal iodine excess,[8] similar to the 12.2% reported in this study. Neonates with maternal iodine excess had a 30% higher TSH in an earlier study.[19] However, the majority of cases of subclinical hypothyroidism were transient in nature without any long-term neurocognitive effects,[8] as seen in this study where transient hypothyroidism recovered by 12 weeks in most babies.

The detection of eight new cases with TSH elevation at 12 weeks of age was a significant finding in this study. Repeat maternal UIC levels were also insufficient suggesting a possible role of environmental goitrogens or iodine deficiency as the likely cause. However, the infant UIC levels, breastmilk iodine levels, maternal thyroid function tests and thyroid antibodies, and consecutive maternal urinary iodine levels that could have suggested the likely etiology were not measured in this study. An earlier study had instead reported higher UIC in infants than their mothers that was predicted by the infant's age and breast milk iodine content.[20] It is also uncertain at present if peripartum maternal iodine excess could have triggered thyroid autoimmunity in these babies, as postulated earlier.[9]

Data from most parts of the world show sufficient median UIC levels among school children and pregnant women after mandatory salt iodization, with few reports of excessive UIC during population screening.[4,21,22] The findings of the present study detected that almost a fourth of the pregnant females with high UIC (>500 ug/L), probably as a result of topical iodine exposure during peripartum period which can result in up to seven times elevation of urinary iodine levels.[23] The maternal UIC levels were insufficient when tested at 12 weeks in all four groups in this study. The estimation of serial urine samples for iodine excretion could have provided information on true iodine excess (not transient) in pregnant mothers. A timed-24-hour sample would have measured UIC with greater precision with lesser individual variations.[24]

The role of thyroid hormones in predicting short and long-term growth in preterm babies has been investigated earlier. The postnatal supplementation of thyroxine for transient hypothyroxinemia was not associated with any beneficial outcomes in preterm babies suggesting it to be a body's adaptive response to sickness or prematurity.[25] The present study also detected 4.5% of babies with hypothyroxinemia (with maternal iodine excess) that was transient in the majority and did not affect the developmental scores. The increased iodine excretion itself could likely have been transient in nature as most mothers normalized the iodine excretion at 12 weeks without a change of dietary habits or residence.

The use of qualitative urinary iodine screening, the lack of serial urinary estimations in the post-partum period, the lack of objective data on dietary iodine consumption and maternal thyroid function status were perceived as limitations of this study. The urinary iodine excretion of newborns was not evaluated as urine collection is cumbersome and difficult at this age. The findings of this study can be assumed to be reassuring for short-term effects, but further studies may be needed to determine the risk of thyroid autoimmunity and long-term effects in the post-iodization era.

To conclude, transient hypothyroxinemia in babies at birth did not impact growth and developmental outcomes at three months of age.

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