Women with high early pregnancy urinary iodine levels have an increased risk of hyperthyroid newborns: the population-based Generation R Study

Short title: Maternal iodine status and thyroid dysfunction

Marco Medici 1,2, Akhgar Ghassabian 1,3, Willy Visser 4, Sabine M P F de Muinck Keizer-Schrama 5, Vincent V W Jaddoe 1,6,7, W Edward Visser 2, Herbert Hooijkaas 8, Albert Hofman 7, Eric A P Steegers 4, Jacoba J Bongers-Schokking 5, H Alec Ross 9, Henning Tiemeier 3,7, Theo J Visser 2, Yolanda B de Rijke 2,10, Robin P Peeters 2

1 The Generation R Study Group and Departments of 2 Internal Medicine, 7 Epidemiology, 8 Immunology; Erasmus Medical Center, Dr Molewaterplein 50, 3000 CA, Rotterdam, The Netherlands
Departments of 3 Child and Adolescent Psychiatry, 4 Obstetrics and Gynecology, 5 Endocrinology, 6 Pediatrics, 10 Clinical Chemistry; Erasmus Medical Center – Sophia Children’s Hospital, Dr Molewaterplein 60, 3000 CB, Rotterdam, The Netherlands
9 Department of Laboratory Medicine; Radboud University Nijmegen Medical Centre, Geert Grootenplein 8, 6525 GA, Nijmegen, The Netherlands

Correspondence:
Robin P Peeters, MD, PhD
Room D 430, Department of Internal Medicine
Erasmus Medical Center

Dr Molewaterplein 50
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3015 GE, Rotterdam, The Netherlands

Tel: +31-10-4635463
Fax: +31-10-7035430
E-mail: r.peeters@erasusmc.nl

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DISCLOSURE STATEMENT: Nothing to declare.
Abstract

Objective: Iodine deficiency during pregnancy results in thyroid dysfunction and has been associated with adverse obstetric and fetal effects, leading to worldwide salt iodisation programs. As nowadays 69% of the world’s population lives in iodine-sufficient regions, we investigated the effects of variation in iodine status on maternal and fetal thyroid (dys)function in an iodine-sufficient population.

Design, Participants and Measurements: Urinary iodine, serum TSH, free T4 (FT4) and TPO-antibody levels were determined in early pregnancy (13.3 (1.9) wk; mean (SD)) in 1098 women from the population-based Generation R Study. Newborn cord serum TSH and FT4 levels were determined at birth.

Results: The median urinary iodine level was 222.5 μg/L, indicating an iodine-sufficient population. 30.8% and 11.5% had urinary iodine levels <150 and >500 μg/L, respectively. When comparing mothers with urinary iodine levels <150 vs ≥150 μg/L, and >500 vs ≤500 μg/L, there were no differences in the risk of maternal increased or decreased TSH, hypothyroxinemia, or hyperthyroidism. Mothers with urinary iodine levels >500 μg/L had a higher risk of a newborn with decreased cord TSH levels (5.6±1.4 (mean±SE) vs 2.1±0.5 %, P = 0.04), as well as a higher risk of a hyperthyroid newborn (3.1±0.9 vs 0.6±0.3 %, P = 0.02). These mothers had newborns with higher cord FT4 levels (21.7±0.3 vs 21.0±0.1 pmol/L, P = 0.04).

Conclusions: In an iodine-sufficient population, higher maternal urinary iodine levels are associated with an increased risk of a hyperthyroid newborn.

Introduction

Iodine is a trace element, which is essential for the synthesis of thyroid hormone (TH). Both iodine deficiency and excess can lead to thyroid dysfunction. Iodine requirements increase during pregnancy due to increased maternal urinary iodide excretion, TH production and placental transfer and metabolism of TH. Iodine deficiency in pregnancy is associated with poor obstetric outcomes, such as spontaneous abortion, prematurity and stillbirth. Furthermore, iodine deficiency in pregnancy...
is related to a wide range of adverse fetal effects as well, such as congenital anomalies, decreased intelligence, and neurological cretinism, which includes spasticity, deaf mutism, and mental retardation. Therefore, the World Health Organization (WHO) recommends a higher iodine intake during pregnancy. Limited data are available on the effects of iodine excess during pregnancy, but it has been shown that in Asian populations excessive intake of iodine-rich water and food (e.g., seaweed) can lead to maternal subclinical hypothyroidism and newborn hypothyroidism. Most of the studies on the effects of iodine status on pregnancy and child development have been performed in iodine-deficient populations. As iodine intake is highly variable within populations, even iodine-sufficient populations can contain subgroups with iodine deficiency or excess. In this context it is remarkable to note that limited data on the effects of variation in iodine status on maternal and fetal TH levels are available from iodine-sufficient pregnant populations. For these reasons, we studied the effects of early pregnancy iodine status on mean maternal and newborn TSH and free T4 (FT4) levels, as well as on the risk of maternal and newborn hypothyroidism, hypothyroxinemia and hyperthyroidism in an iodine-sufficient population.

Materials and methods

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards in Rotterdam, the Netherlands, which has been described in detail previously. Mothers with a delivery date between April 2002 and January 2006 were enrolled in the study. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants.

Population for analysis

TSH, FT4 and thyroid peroxidase antibody (TPOAb) levels were determined in 5326 pregnant women. Due to financial constraints, urinary iodine levels were determined in a random subset of these women (n = 1154). Women with known thyroid disease, thyroid medication or thyroid interfering medication (such as amiodarone) were excluded (n = 14). Twin pregnancies (n = 27) and...
pregnancies after fertility treatment (n = 15) were also excluded. In total, 1098 women were included in one or more analyses. Cord serum TSH and FT4 levels were determined in 1068 of their newborns.

*Thyroid parameter measurements*

Maternal serum samples were obtained in early pregnancy (mean (SD): 13.3(1.9) wk), and cord serum samples were obtained at birth (40.1(1.5) wk). TSH and FT4 were determined in maternal and cord samples using chemiluminescence assays (Vitros ECI; Ortho Clinical Diagnostics, Rochester, NY). The intra- and interassay coefficients of variation were <4.1% for TSH and <5.4% for FT4. Maternal TPOAbs were measured using the Phadia 250 immunoassay (Phadia AB, Uppsala, Sweden) and regarded as positive when > 60 IU/ml.

*Iodine measurements*

Maternal serum and urinary samples were obtained at the same time (mean (SD): 13.3(1.9) wk). Urinary iodine concentrations were determined in a random subset of 1154 women in which thyroid parameters were determined. Urinary iodine was measured through the ceri-arsenite reaction following destruction by means of ammoniumpersulphate. After brief centrifugation, sodium arsenite solution (0.1 mol/L in 1 mol/L of sulphuric acid) was added. Subsequently, ceriammonium sulphate was added and colour was allowed to develop at 250 C during 60 minutes. Optical density was assessed at 405 nm. At a level of 1.7 µmol/L iodine the within-assay CV was 5.1% and the between-assay CV was 14.3%.

Of note, none of the urine samples were tested by test strips before iodine concentrations were determined. To assess the iodine status of a population, the WHO recommends the use of the median (not the mean) urinary iodine concentration in the population, as urinary iodine concentrations are influenced by recent iodine intake. For pregnant populations, the WHO regards median urinary iodine levels of < 150 µg/L as insufficient, 150 – 249 µg/L as adequate, and > 500 µg/L as excessive.

*Covariates*

Information about maternal age, socioeconomic status (SES), ethnicity, thyroid disease, thyroid (interfering) medication usage and first trimester vomiting was obtained by questionnaires during
pregnancy. SES was defined by educational level, net household income, and employment status. Information on fertility treatment was obtained from midwives and obstetricians. At enrolment, maternal height and weight were measured to calculate body mass index (BMI, kg/m$^2$). Ultrasound measurements were used to establish gestational age in early pregnancy (planned at gestational age 12 wks).

Statistical analysis

The Endocrine society and American Thyroid Association guidelines recommend the use of population-specific serum thyroid hormone reference ranges during pregnancy, as various studies have shown substantial differences between populations in thyroid hormone reference ranges during pregnancy. We therefore calculated reference ranges for maternal and cord TSH and FT4 levels in our own population. These were defined as the range between the 2.5th and 97.5th percentiles, after exclusion of women with known thyroid disease, thyroid (interfering) medication usage, twin pregnancies, and pregnancies after fertility treatment. Maternal reference ranges were 0.02 - 4.10 mU/L for TSH, and 10.3 – 22.0 pmol/L for FT4, and cord reference ranges were 3.10 – 33.00 mU/L for TSH, and 15.4 – 30.1 pmol/L for FT4. For mothers and newborns, increased TSH (including both subclinical and overt hypothyroidism) was defined as a TSH above the reference range. Similarly, hypothyroidism was defined as a high TSH with a low FT4, and hypothyroxinemia as a low FT4 with a normal TSH. Decreased TSH (including both subclinical and overt hyperthyroidism) was defined as a low TSH, and hyperthyroidism as a low TSH with a high FT4.

Median maternal urinary iodine levels were calculated, and subgroups were identified with low (<150 μg/L) and high (>500 μg/L) urinary iodine levels. We studied the relations between urinary iodine <150 μg/L vs ≥150 μg/L groups and the risk of increased maternal TSH levels and hypothyroxinemia. The associations between urinary iodine >500 μg/L vs ≤500 μg/L groups and the risk of increased maternal TSH levels and hypothyroxinemia were also studied, as higher urinary iodine levels have previously been associated with maternal subclinical hypothyroidism. We additionally investigated the relations between urinary iodine >500 μg/L vs ≤500 μg/L groups and the risk of decreased maternal TSH levels and hyperthyroidism. Analyses were
performed using logistic regression. Maternal TSH and FT4 levels in these groups were compared using AN(C)OVA. To achieve normal distribution, TSH was transformed by the natural logarithm. Analyses were adjusted for gestational age at urine / serum sampling, and repeated in TPOAb-negative mothers only, additionally adjusting for maternal age, SES, ethnicity, BMI, and vomiting. We furthermore studied the relations between urinary iodine <150 μg/L vs ≥150 μg/L groups and the risk of increased cord TSH levels and newborn hypothyroxinemia. The associations between urinary iodine >500 μg/L vs ≤500 μg/L groups and the risk of increased cord TSH levels and hypothyroxinemia were also studied, as high maternal iodine intake has previously been associated with newborn hyperthyrotropinemia.\textsuperscript{13} As mean cord FT4 levels were found to be higher in mothers with urinary iodine >500 μg/L, we additionally studied the relations between urinary iodine >500 μg/L vs ≤500 μg/L groups and the risk of decreased cord TSH levels and newborn hyperthyroidism. Cord TSH and FT4 levels in these groups were compared using AN(C)OVA. Analyses were adjusted for gestational age at urine / serum sampling, and gestational age at birth. Analyses were repeated in TPOAb-negative mothers only, adjusting for maternal age, SES, ethnicity, BMI, and vomiting, as well as for maternal TSH and FT4 levels.

**Results**

Characteristics of the study population are shown in Table 1. There were 28 mothers with an increased TSH, 1 hypothyroid mother, 26 hypothyroxinemic mothers, 27 mothers with a decreased TSH, and 12 hyperthyroid mothers. There were 28 newborns with an increased TSH, 1 hypothyroid newborn, 26 hypothyroxinemic newborns, 27 newborns with a decreased TSH, and 10 hyperthyroid newborns.

**Maternal urinary iodine distribution**

The maternal urinary iodine distribution for the current study is shown in Fig.1. Urinary iodine levels ranged from 9.3 to 1743.5 μg/L, with a median level of 222.5 μg/L. This population is therefore regarded iodine-sufficient.\textsuperscript{7} 30.8% of the mothers had a urinary iodine level < 150 μg/L, and 11.5% had a urinary iodine level > 500 μg/L.

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Low and high maternal urinary iodine levels vs maternal thyroid status

As shown in Table 2, mothers with urinary iodine levels < 150 μg/L did not differ in their risk of having increased TSH levels or hypothyroxinemia, compared to mothers with urinary iodine levels ≥ 150 μg/L. No differences in maternal TSH (1.48±0.06 vs 1.52±0.04 mU/L, P = 0.56) or FT4 (15.0±0.2 vs 14.9±0.1 pmol/L, P = 0.93) levels were found either. Mothers with urinary iodine levels > 500 μg/L did not differ in their risk of having increased TSH levels (2.6±0.5 vs 2.4±1.4 %, P = 0.95) or hypothyroxinemia (2.3±0.5 vs 3.2±1.3 %, P = 0.43). As shown in Table 2, these mothers had a higher risk of decreased TSH levels, but this effect failed to reach statistical significance (P = 0.08). There were no differences in the risk of maternal hyperthyroidism, neither after exclusion of TPOAb-positive mothers and adjustment for confounders (Table 2). Nor were there differences in mean maternal TSH (1.45±0.09 vs 1.52±0.03 mU/L, P = 0.17) or FT4 (14.9±0.3 vs 15.0±0.1 pmol/L, P = 0.81) levels.

Low and high maternal urinary iodine levels vs newborn thyroid status

As shown in Table 3, mothers with urinary iodine levels < 150 μg/L did not differ in their risk of having newborns with increased TSH levels or hypothyroxinemia, compared to mothers with urinary iodine levels ≥ 150 μg/L. No differences in cord TSH (11.83±0.43 vs 11.44±0.28 mU/L, P = 0.17) or FT4 (21.0±0.2 vs 21.1±0.1 pmol/L, P = 0.77) levels were found either. Mothers with urinary iodine levels > 500 μg/L also did not differ in their risk of having newborns with increased TSH levels (2.9±0.5 vs 0.7±1.4 %, P = 0.20) or hypothyroxinemia (2.7±0.5 vs 0.8±1.4 %, P = 0.24). However, these mothers had newborns with higher cord FT4 levels (21.7±0.3 vs 21.0±0.1 pmol/L, P = 0.04), which remained significant after exclusion of TPOAb-positive mothers and adjustment for confounders (21.8±0.3 vs 21.0±0.1 pmol/L, P = 0.04), as well as after additional adjustment for maternal TSH and FT4 levels (21.8±0.3 vs 21.0±0.1 pmol/L, P = 0.03). We therefore also studied the relations with newborn decreased TSH levels and hyperthyroidism. Table 3 shows that these women with urinary iodine levels > 500 μg/L had a higher risk of a newborn with decreased cord TSH levels, as well as an increased risk of a hyperthyroid newborn (Table 3). These effects remained significant after exclusion of TPOAb-positive mothers and adjustment for confounders, as
well as after additional adjustment for maternal TSH and FT4 levels. Exclusion of women with low urinary iodine levels (< 150 μg/L) from these analyses, thereby comparing women with urinary iodine levels > 500 with 150-500 μg/L, resulted in a similar increased risk of a newborn with decreased cord TSH levels (5.6±1.5 vs 2.3±0.7 %), which failed to reach statistical significance (P = 0.06), whereas the increased risk of a hyperthyroid newborn remained significant (3.1±0.8 vs 0.3±0.4 %, P = 0.01).

No interactions between gestational age at birth and maternal urinary iodine levels on the risk of a newborn with decreased TSH levels or hyperthyroidism were detected ((gestational age * urinary iodine) interaction term P-values of 0.22 and 0.62, respectively).

**Discussion**

In the current study, we investigated in an iodine-sufficient population the relation of maternal iodine status and abnormal maternal and cord thyroid function tests, and are the first to show that mothers with higher iodine levels have an increased risk of hyperthyroid newborns. The WHO estimates that approximately 69% of the world’s population lives in iodine-sufficient regions. However, limited data from iodine-sufficient populations are available on the effects of low maternal iodine status on maternal and newborn thyroid function. Azizi et al. showed in 123 pregnant women from an iodine-sufficient population that newborn TSH, FT4, T4 and T3 levels did not differ between mothers with urinary iodine levels < 150 μg/L and ≥ 150 μg/L. This is in line with the results from the current study, in which we show that mothers from an iodine-sufficient population with urinary iodine levels < 150 μg/L and ≥ 150 μg/L do not differ in maternal or newborn cord TSH and FT4 levels. We additionally show that there are no differences in the risk of increased TSH and hypothyroxinemia in maternal serum or cord blood.

However, when comparing mothers with urinary iodine levels > 500 μg/L and ≤ 500 μg/L, mothers with urinary iodine levels > 500 μg/L had a 2.6 times increased risk of a newborn with decreased cord TSH levels, and a 4.9 times increased risk of a hyperthyroid newborn. These effects remained significant after taking account of a number of potentially interfering factors, including maternal TPOAb status, age, SES, ethnicity, BMI, and vomiting, as well as maternal serum TSH and FT4.
levels. When comparing women with urinary iodine levels > 500 with 150-500 μg/L, a similar increased risk of a newborn with decreased cord TSH levels was observed. However, this effect failed to reach statistical significance ($P = 0.06$), which could be due to a lack of statistical power due to the exclusion of the large group of women with urinary iodine levels < 150 μg/L (i.e., 30.8% of the total population). After exclusion of this group, a 9.6 times increased risk of a hyperthyroid newborn remained significant. Various studies have shown that fetal hyperthyroidism is associated with fetal loss, intrauterine growth restriction, and premature birth \(^{22}\). Fetal hyperthyroidism is also associated with a wide range of neonatal complications, such as heart failure, cardiac arrhythmia, poor weight gain, and thrombocytopenia \(^{22, 23}\).

We did not observe any differences in mean maternal TSH and FT4 levels between mothers with urinary iodine levels > 500 μg/L and ≤ 500 μg/L. There was a trend towards a higher risk of maternal decreased TSH in mothers with urinary iodine levels > 500 μg/L, but this effect failed to reach statistical significance, and neither were there differences in the risk of maternal hyperthyroidism. It has been shown that higher urinary iodine levels in Chinese and Japanese pregnant women are associated with an increased risk of maternal subclinical hypothyroidism \(^{14, 24}\). Furthermore, Japanese women consuming large quantities of iodine-rich seaweed have been reported to have an increased risk of newborns with transient hypothyroidism or persistent hyperthyrotropinemia \(^{13}\). We did not find an effect of higher maternal urinary iodine levels on the risk of maternal or newborn increased TSH levels or hypothyroxinemia in the current study. This may be explained by the fact that the maximum urinary iodine levels in these Chinese and Japanese populations were much higher compared to the current study, leading to hypothyroidism as a result of failure to escape from the acute Wolff-Chaikoff effect \(^{14, 25, 26}\).

A number of potential mechanisms could explain the observed association between high maternal early pregnancy iodine status and the increased risk of a hyperthyroid newborn. The fact that no effects of high maternal iodine status on maternal thyroid status were detected, and associations with the risk of newborn hyperthyroidism remained significant after adjustment for maternal thyroid status, suggests that especially the fetal thyroid is not able to deal with the high iodine status. Studies have

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shown that, postnatally, the thyroid gland is able to deal with variation in iodide supply by adjusting iodide uptake via regulation of the expression of the sodium-iodide symporter (NIS)\textsuperscript{27, 28}. However, limited data are available about the regulation of iodine uptake in the fetal thyroid gland. To study if maturity of the fetal thyroid could be a factor, we additionally studied the interaction between gestational age at birth and high maternal iodine levels on the risk of newborn decreased cord TSH levels or hyperthyroidism. Although we did not find a significant effect, it would be interesting to further explore this relation in large cohorts of premature pregnancies.

An alternative explanation of the increased risk of hyperthyroid newborns in mothers with a high iodine status could be that mothers with (subclinical) Graves’ disease, which may develop earlier when iodine is high\textsuperscript{29}, were overrepresented in this group. Mothers with Graves’ disease have an increased risk of hyperthyroid newborns due to transplacental passage of thyroid stimulating immunoglobulins\textsuperscript{30}. However, the fact that no associations with maternal serum TSH and FT4 levels were found, nor with the risk of maternal hyperthyroidism, makes this explanation highly unlikely. Taken together, the exact mechanism underlying the observed association between high maternal early pregnancy iodine status and the increased risk of hyperthyroid newborns therefore remains to be clarified in future studies, taking fetal thyroid gland compensatory mechanisms for abnormal iodide supply into account.

Various studies have shown substantial differences between populations in the prevalence of TPOAb-positivity during pregnancy\textsuperscript{31-33}. In the current study, we found a prevalence of 6.1 %, which is low compared to other populations\textsuperscript{32, 33}. Although a similar low frequency (i.e. 5.7%) has previously been found in another large multi-ethnic pregnant population from the Netherlands\textsuperscript{31}, the exact reasons of these differences in TPOAb-positivity prevalences remain to be clarified.

We are aware of a number of potential limitations of the current study. Maternal urinary iodine levels were only measured once. As individual iodine status can be influenced by recent food intake, multiple urinary iodine measurements will give a better estimation of the average iodine status of an individual\textsuperscript{34, 35}. Given the relatively large size of our population, we assume that the groups with higher and lower iodine levels will on average have a higher and lower iodine status too. However,
this intra-individual variation in iodine levels may have led to an underestimation of the observed effect sizes. Furthermore, we show that a higher maternal iodine status is associated with an increased risk of biochemical newborn hyperthyroidism, but did not study the effects on detrimental pregnancy and postnatal outcomes associated with newborn hyperthyroidism. The current study was underpowered to do so, given the relatively low prevalence of newborn hyperthyroidism or decreased TSH levels. However, various other studies have convincingly shown an increased risk of a wide range of pregnancy and neonatal complications in newborn hyperthyroidism. Finally, no data were available on potential exposure to iodinated radiographic contrast.

Since 1990, international and national authorities have taken concerted action to eliminate iodine deficiency disorders using salt iodisation as the main strategy. The Netherlands also has a long history of iodine fortification programs, the most important of which include iodised bread salt and table salt. The focus of most iodine studies in pregnant women has been on the detrimental effects of maternal iodine deficiency during pregnancy. Given the worldwide implementation of iodine fortification programs, it is remarkable to note that limited data are available about the effects of high maternal iodine levels during pregnancy and newborn thyroid status. To our knowledge, this is the first study in an iodine-sufficient population on the risk of newborn thyroid dysfunction in mothers with a higher iodine status. The current study was performed in a pregnant population, whose iodine status is regarded adequate, not excessive, by the internationally recognized WHO criteria. Despite this, we identified a substantial subgroup (i.e., 11.5% of the general pregnant population) with higher urinary iodine levels, which had a considerable increased risk of a hyperthyroid newborn. This group consisted of more non-Westerns (46.0±4.2 vs 31.5±1.5 %, $P = 0.001$), and less subjects with a high SES (35.4±4.7 vs 48.2±1.7 %, $P = 0.01$). However, the observed effects remained significant after correction for these factors. A potential source of the high iodine status could be the intake of iodine-containing supplements. For the Dutch mothers we had data available on whether supplements were taken during pregnancy. The intake of iodine-containing supplements was compared between mothers with urinary iodine levels $> 500$ μg/L and $\leq 500$ μg/L, but no differences were found (16.9±5.8 vs 20.9±1.8 %, $P = 0.51$). However, no data were available on the frequency and number of tablets that...
were taken. Therefore, the origin of the higher iodine levels should be clarified in future studies, taking the role of dietary patterns into account. Irrespective of the exact cause of these higher iodine levels, our results suggest that, in iodine-sufficient populations, it may be of interest to closer monitor this large group of pregnant women with a higher iodine status as well.

In conclusion, we show that in an iodine-sufficient population, mothers with higher iodine levels have an increased risk of hyperthyroid newborns. These data provide insight into the effects of variation in maternal early pregnancy iodine status on maternal and fetal thyroid status. Furthermore, these data should prompt further studies on the identification and closer monitoring of this subgroup of mothers with a higher iodine status during early pregnancy.

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**Figure legends**

Figure 1 Early pregnancy urinary iodine levels in 1098 pregnant women. Levels ranged from 9.3 – 1743.5 μg/L, with a median level of 222.5 μg/L. 30.8% had an urinary iodine level < 150 μg/L, and 11.5% had an urinary iodine level > 500 μg/L.

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Table 1: Population characteristics of 1098 pregnant women from the Generation R Study

<table>
<thead>
<tr>
<th>Characteristic (n = 1098)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>29.9 (5.0)</td>
</tr>
<tr>
<td>Maternal ethnicity (% western) b</td>
<td>65.6%</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10.2%</td>
</tr>
<tr>
<td>Middle</td>
<td>42.9%</td>
</tr>
<tr>
<td>High</td>
<td>46.9%</td>
</tr>
<tr>
<td>Maternal vomiting (%) b</td>
<td>50.0%</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>24.3 (4.4)</td>
</tr>
<tr>
<td>Gestational age at maternal blood / urine sampling (weeks)</td>
<td>13.3 (1.9)</td>
</tr>
<tr>
<td>Maternal TSH (mU/L, median (IQR))</td>
<td>1.29 (0.81,1.96)</td>
</tr>
<tr>
<td>Maternal FT4 (pmol/L)</td>
<td>14.9 (3.4)</td>
</tr>
<tr>
<td>Maternal TPOAb-positivity (%)</td>
<td>6.1%</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>40.1 (1.5)</td>
</tr>
<tr>
<td>Cord TSH (mU/L, median (IQR)) c</td>
<td>9.42 (6.38,14.30)</td>
</tr>
<tr>
<td>Cord FT4 (pmol/L) c</td>
<td>21.1 (3.7)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; FT4, free T4; TPOAb, thyroid peroxidase antibody;

b Ranging from less than once a week to daily vomiting; 20.0% reported to vomit more than once a week, and 9.1% on a daily basis.

c Cord TSH and FT4 levels were available in 1068 newborns.

51.9% Dutch, 10.1% Surinam/Antillean, 8.6% Turkish, 7.2% Moroccan, 13.7% Other Western, 8.5% Other non-Western.
Table 2. Maternal early pregnancy urinary iodine levels vs the risk of maternal thyroid dysfunction.

<table>
<thead>
<tr>
<th>Maternal urinary iodine level (μg/L)</th>
<th>Maternal urinary iodine level (μg/L)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased maternal TSH levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1(^a) (% (SE))</td>
<td>1.5 (0.9)</td>
<td>3.0 (0.6)</td>
<td>0.47 (0.18-1.25)</td>
</tr>
<tr>
<td>Model 2(^b) (% (SE))</td>
<td>1.1 (0.8)</td>
<td>2.2 (0.5)</td>
<td>0.53 (0.17-1.63)</td>
</tr>
</tbody>
</table>

| Decreased maternal TSH levels       |                                     |             |    |
| Model 1\(^a\) (\% (SE))             | 2.2 (0.5)                           | 4.8 (1.4)   | 2.29 (0.91-5.80) | 0.08 | Model 1\(^a\) (\% (SE)) | 1.1 (0.3) | 0.8 (0.9) | 0.73 (0.09-5.68) | 0.76 |
| Model 2\(^c\) (\% (SE))             | 2.1 (0.5)                           | 4.8 (1.4)   | 2.43 (0.91-6.51) | 0.08 | Model 2\(^c\) (\% (SE)) | 1.1 (0.3) | 0.9 (1.0) | 0.98 (0.12-8.31) | 0.99 |
Table 3. Maternal early pregnancy urinary iodine levels vs the risk of newborn thyroid dysfunction.

<table>
<thead>
<tr>
<th>Maternal urinary iodine level (μg/L)</th>
<th>Maternal urinary iodine level (μg/L)</th>
<th>Newborn hypothyroxinemia</th>
<th>Newborn hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased newborn TSH levels</strong></td>
<td></td>
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</tr>
<tr>
<td>Model 1 a (%, mean (SE))</td>
<td>Model 1 a (%, mean (SE))</td>
<td>3.6 (0.9)</td>
<td>2.2 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.72 (0.80-3.69)</td>
<td>1.76 (0.79-3.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Model 2 b (%, mean (SE))</td>
<td>Model 2 b (%, mean (SE))</td>
<td>3.5 (0.9)</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.68 (0.74-3.79)</td>
<td>1.71 (0.73-4.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>Model 3 c (%, mean (SE))</td>
<td>Model 3 c (%, mean (SE))</td>
<td>3.6 (1.0)</td>
<td>2.2 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.69 (0.75-3.84)</td>
<td>1.79 (0.76-4.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Decreased newborn TSH levels</strong></td>
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<tr>
<td>Model 1 a (%, mean (SE))</td>
<td>Model 1 a (%, mean (SE))</td>
<td>2.1 (0.5)</td>
<td>5.6 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.58 (1.07-6.25)</td>
<td>4.87 (1.35-17.57)</td>
</tr>
<tr>
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<td></td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 2 b (%, mean (SE))</td>
<td>Model 2 b (%, mean (SE))</td>
<td>2.1 (0.5)</td>
<td>5.8 (1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.71 (1.07-6.87)</td>
<td>6.76 (1.58-28.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 3 c (%, mean (SE))</td>
<td>Model 3 c (%, mean (SE))</td>
<td>2.1 (0.5)</td>
<td>5.9 (1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.66 (1.04-6.78)</td>
<td>9.24 (1.76-48.44)</td>
</tr>
<tr>
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<td>0.04</td>
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</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared). Increased and decreased newborn TSH levels were defined as serum TSH > 33.00 and serum TSH < 3.10 mU/L, respectively. Newborn hypothyroxinemia was defined as serum TSH 3.10 – 33.00 mU/L and FT4 < 15.4 pmol/L. Newborn hyperthyroidism was defined as serum TSH < 3.10 mU/L and FT4 > 30.1 pmol/L.

a Adjusted for gestational age at urine/plasma sampling and gestational age at birth.
b Thyroid peroxidase antibody (TPOAb) positives excluded, adjusted for maternal age, socioeconomic status (SES), ethnicity, BMI, and vomiting (performed in 311 and 691 mothers with urinary iodine levels < 150 and ≥ 150 μg/L, respectively, and 116 and 886 mothers with urinary iodine levels > 500 and ≤ 500 μg/L, respectively).
c TPOAb-positives excluded, adjusted for maternal age, SES, ethnicity, BMI, and vomiting, as well as for maternal serum TSH and FT4 levels (performed in 306 and 684 mothers with urinary iodine levels < 150 and ≥ 150 μg/L, respectively, and 113 and 877 mothers with urinary iodine levels > 500 and ≤ 500 μg/L, respectively).
Fig. 1. Early pregnancy urinary iodine distribution in 1098 pregnant women from the Generation R Study.

Fig. 1. Early pregnancy urinary iodine levels in 1098 pregnant women. Levels ranged from 9.3 - 1743.5 μg/L, with a median level of 222.5 μg/L. 30.8% had an urinary iodine level <150 μg/L, and 11.5% had an urinary iodine level >500 μg/L.