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Clinical Research Article

Association of Isolated Hypothyroxinemia and Subclinical Hypothyroidism With Birthweight: A Cohort Study in Japan

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Abstract

Context: Isolated hypothyroxinemia (low maternal free thyroxine [FT4] in the absence of thyroid-stimulating hormone [TSH] elevation) and subclinical hypothyroidism (high TSH in the absence of FT4 elevation) during early pregnancy are common. However, there are limited data regarding pregnancy outcomes, particularly their association with birthweight.

Objective: We assessed the association between isolated hypothyroxinemia and subclinical hypothyroidism during the first trimester and birthweight.

Methods: Analyses were conducted using a database of pregnant women (n = 1105; median age, 35 years) who delivered at the National Center for Child Health and Development, a tertiary hospital in Tokyo. The primary outcomes included the rates of small for gestational age (SGA), large for gestational age (LGA), and low birth weight.

Results: Of the 1105 pregnant women, 981 were classified into the euthyroidism group, 25 into the isolated hypothyroxinemia group, and 26 into the subclinical hypothyroidism group during the first trimester. The prevalence of SGA was significantly higher in isolated hypothyroxinemia and subclinical hypothyroidism groups than the euthyroidism group (28.0% and 19.2%, respectively, vs 5.7%; $P < .01$). The odds ratio with 95% CI for SGA was 12.51 (4.41-35.53) for isolated hypothyroxinemia and 4.44 (1.57-12.56) for subclinical hypothyroidism in a multivariable adjustment model. Isolated hypothyroxinemia and subclinical hypothyroidism were not significantly associated with LGA and low birth weight.

Conclusion: Pregnant women with isolated hypothyroxinemia and subclinical hypothyroidism in the first trimester have an increased likelihood of SGA. Screening and careful perinatal checkups for isolated hypothyroxinemia and subclinical hypothyroidism may help identify pregnant women at high risk for SGA.

Key Words: isolated hypothyroxinemia, subclinical hypothyroidism, thyroid hormones, small for gestational age, pregnancy outcome

Abbreviations: BMI, body mass index; FT4, free thyroxine; hCG, human chorionic gonadotropin; IQR, interquartile range; LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age; TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

Thyroid hormones play an indispensable role in fetal growth and development throughout the gestational period, particularly during early pregnancy [1]. Physiologically, in the first trimester, maternal free thyroxine (FT4) concentration increase, and thyroid-stimulating hormone (TSH) concentrations decrease due to increased human chorionic gonadotropin (hCG) concentrations [2]. These hormonal changes are required in response to increasing maternal metabolic demands and to adequately supply T4 to the fetus. During the first trimester, fetal thyroid hormone availability completely depends on the transplacental passage of maternal hormones. Thus, thyroid hormone abnormalities in the first trimester may lead to adverse pregnancy outcomes.

Subclinical hypothyroidism is defined as increased TSH with normal FT4 levels, and isolated hypothyroxinemia is defined as reduced FT4 with normal TSH levels. Subclinical hypothyroidism and isolated hypothyroxinemia are prevalent thyroid hormone abnormalities during early pregnancy. Dong et al showed the prevalence of subclinical hypothyroidism and isolated hypothyroxinemia is 3.47% and 2.05% respectively in their meta-analysis [3]. The adverse pregnancy outcomes associated with subclinical hypothyroidism, including preterm birth and small for gestational age (SGA), have been reported [4, 5]. However, the pregnancy outcomes associated with isolated hypothyroxinemia are inconsistent [5, 6]. The potential reasons for the inconsistent findings include the following: the definition of isolated hypothyroxinemia differed across studies, the cut-off value of FT4 concentrations ranges from the 2.5th to the 10th percentile, and the timing when blood samples were collected for the measurements also varied across studies. Furthermore, iodine deficiency, obesity, and other metabolic factors have been shown to be associated

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with isolated hypothyroxinemia [6]. However, previous studies did not fully adjust for these factors when assessing the association between isolated hypothyroxinemia and pregnancy outcomes.

Using a database of pregnant women who delivered at the National Center for Child Health and Development, a tertiary hospital in Tokyo, we assessed whether subclinical hypothyroidism and isolated hypothyroxinemia in the first trimester were associated with pregnancy outcomes, including SGA, large for gestational age (LGA), and low birth weight. In addition, we assessed whether these associations were attenuated after adjusting for factors associated with subclinical hypothyroidism and isolated hypothyroxinemia, including iodine deficiency, obesity, and metabolic factors.

Materials and Methods

Design of a Prospective Cohort Study

This prospective single-center birth cohort study was performed within the Seiiku Boshi Cohort [7]. A total of 4164 pregnant women in their first trimester were recruited during their antenatal visits to the National Center for Child Health and Development (NCCHD) from May 13, 2010, to November 28, 2013. NCCHD is a tertiary hospital in Tokyo that manages approximately 2000 annual deliveries. Written consent was obtained from 2310 women who participated in this study. The study protocol was approved by the Institutional Review Board of NCCHD on August 2, 2010 (Study ID: H22-417).

Population for Analyses

Data on TSH and FT4 levels within the first trimester and antithyroid peroxidase antibody (TPOAb), antithyroglobulin antibody (TgAb), and urinary iodine concentrations during the second trimester were available for 1458 singleton pregnant women. Women who withdrew their consent (n = 1), with pre-existing thyroid disease including levothyroxine therapy prior to conception (n = 54), assisted reproductive technology pregnancies, in vitro fertilization, and intracytoplasmic sperm injection (n = 275), and both pre-existing thyroid disease and assisted reproductive technology pregnancies (n = 23) were excluded. Among the 1105 eligible participants, women categorized as having euthyroidism, isolated hypothyroxinemia, or subclinical hypothyroidism were analyzed (Fig. 1).

Data Collection

Maternal sociodemographic data, biological data, and medical history were collected using a self-reported questionnaire. TSH and FT4 levels collected in the first trimester were quantified using a chemiluminescent enzyme immunoassay kit (LUMIPULSE Analyzer; Fujirebio, Tokyo, Japan). The reference ranges by the manufacturer were 0.746 to 4.118 mU/L for TSH and 8.75 to 15.44 pmol/L for FT4. We used the cohort-specific TSH and FT4 cutoff values, 2.5th to 97.5th percentile, for the diagnosis of euthyroidism, isolated hypothyroxinemia, and subclinical hypothyroidism. TPOAb and TgAb levels in the second trimester were assessed using radioimmunoassay kits (Cosmic Corporation Co., Ltd., Tokyo, Japan) until March 2010. Both TPOAb and TgAb were determined as positive when the concentrations were greater than 0.3 U/mL, the manufacturer-defined cutoff value. After April 2010, TPOAb and TgAb were assessed using electrochemiluminescence immunoassay kits (Roche Diagnostics K.K., Tokyo, Japan) and were determined to be positive when the concentrations were greater than 16 IU/mL or 28 IU/mL, respectively, according to manufacturer-defined cutoff values. Data on urinary iodine concentrations in the single spot urine and serum hemoglobin A1c collected during the second trimester were also used for analysis. Information on perinatal outcomes was obtained from the medical records. The gestational weight gain was calculated with the prepregnancy body weight in the self-reported questionnaire and the body weight measured at the delivery in the medical records.

Definition for Isolated Hypothyroxinemia and Subclinical Hypothyroidism

Thyroid function test abnormalities were defined according to the cohort-specific 2.5th and 97.5th percentiles of TSH and FT4 concentrations. Isolated hypothyroxinemia was defined as FT4 concentration below the 2.5th percentile and TSH concentration within the normal range. Subclinical hypothyroidism was defined as FT4 concentration within the normal range and TSH concentration above the 97.5th percentile. Overt hypothyroidism was defined as FT4 concentration below the 2.5th percentile and TSH concentration above the 97.5th percentile. Isolated hyperthyroxinemia was defined as an FT4 concentration above the 97.5th percentile and TSH concentration within the normal range. Subclinical hyperthyroidism was defined as FT4 concentration within the normal range and TSH concentration below the 2.5th percentile. Overt hyperthyroidism was defined as FT4 concentration above the 97.5th percentile and TSH concentration below the 2.5th percentile. Euthyroidism was defined as FT4 and TSH concentrations within the normal range.

Definition for Perinatal Outcomes and for Other Characteristics

SGA was defined as neonatal birthweight less than the 10th percentile of the reference curves of birthweight per gestational week. LGA was defined as neonatal birthweight above the 90th percentile of the reference curves of birthweight for gestational weeks. Other variables were defined as follows: preterm birth (birth <37th gestational week), low birth weight (birthweight <2500 g), macrosomia (birthweight ≥4000 g), overweight/obesity (body mass index [BMI] ≥ 25), and underweight (BMI < 18.5). BMI was calculated using maternal body weight prior to pregnancy. Gestational diabetes mellitus was diagnosed if 1 or more plasma glucose measurements exceeded the following thresholds using a 75-g oral glucose tolerance test: fasting level of 92 mg/dL, 1-hour level of 180 mg/dL, and 2-hour level of 153 mg/dL [8]. Hypertensive disorders of pregnancy were defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation [9]. Smokers were defined as women who were declared to be current smokers at the first antenatal visit. Maternal iodine intake status was categorized according to the criteria based on urinary iodine concentrations: insufficient (<150 μg/L), adequate (150-249 μg/L), above requirements (250-499 μg/L), or excessive (≥500 μg/L) [10].

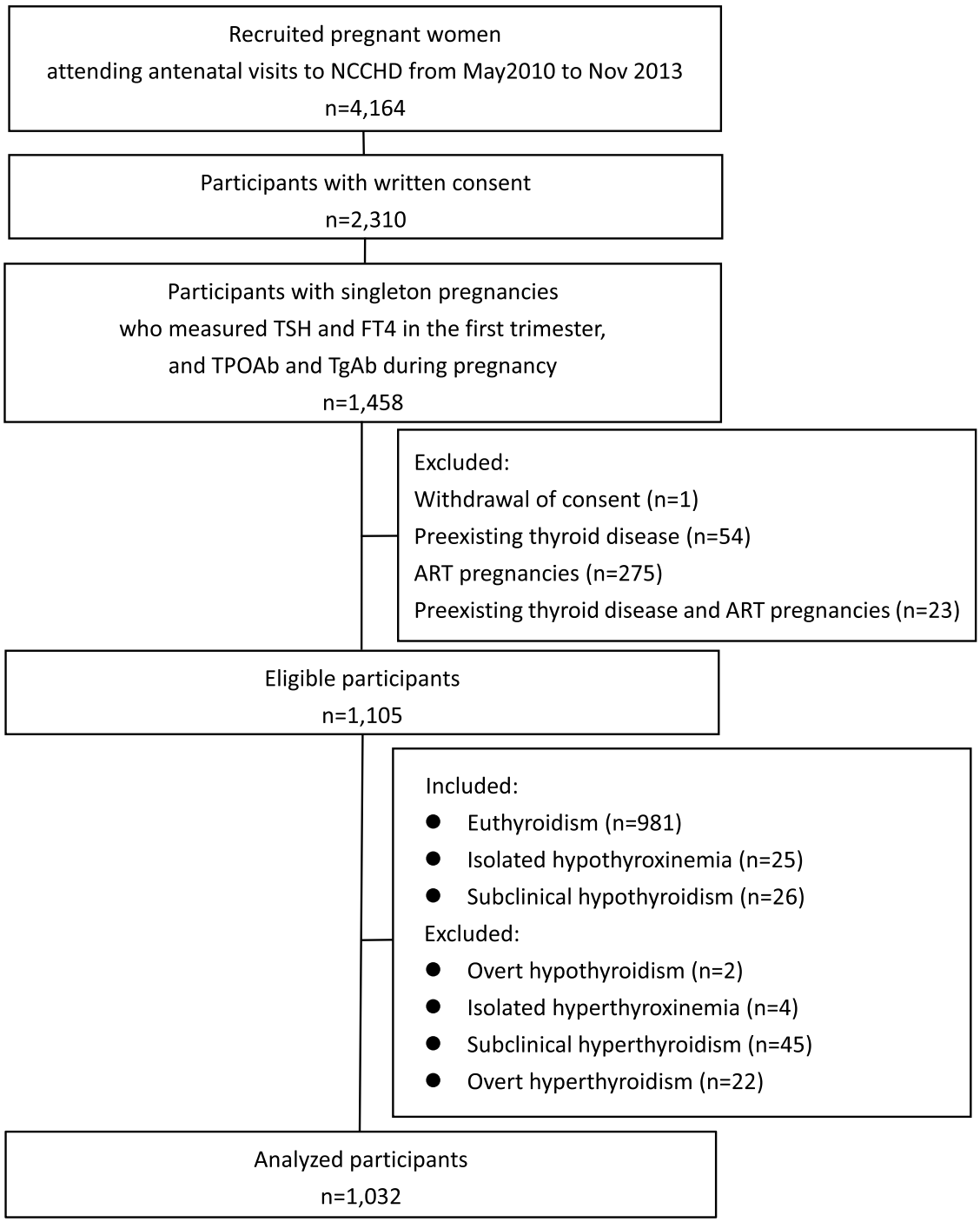

Figure 1. Flow chart of the study population.

Statistical Analysis

Continuous values are presented as median (interquartile range [IQR]), and categorical values are presented as numbers (percentages). Shapiro–Wilk tests were performed to assess the normality of the distribution of each continuous value. Kruskal–Wallis tests were performed using post hoc steel tests. The euthyroid group served as a reference group. Chi-square tests or Fisher's exact tests were performed, as appropriate. Using logistic regression models, we calculated the odds ratios (ORs) and 95% CIs for perinatal outcomes, SGA, LGA, and low birth weight associated with isolated hypothyroxinemia and subclinical hypothyroidism (vs euthyroid), respectively. ORs were calculated in an unadjusted model (Model 1) and after adjustment for maternal age, BMI, smoking, parity, fetal sex, urinary iodine excretion, and TPOAb positivity, gestational weight gain, and gestational weeks at the sampling of thyroid function (Model 2). Covariates were selected a priori because they have been shown to be associated with isolated hypothyroxinemia, subclinical hypothyroidism, and perinatal outcomes [5, 11]. We adjusted for TPOAb positivity but not for TgAb positivity, considering that the association of TgAb positivity with

thyroid function is only driven by concomitant TPOAb positivity in an individual participant data meta-analysis from the Consortium on Thyroid and Pregnancy [12]. We performed sensitivity analysis to exclude the participants who started to take levothyroxine after the measurement of thyroid function. All statistical analyses were performed using JMP Pro 16.0 (SAS Institute Inc., NC, USA). Statistical significance was defined as P-value <.05, using 2-sided tests.

Results

Study Population

A total of 1105 women (median [SD] maternal age, 35 [33-38] years; median [SD] BMI, 20.0 [18.6-21.6] kg/m^2; median [SD] urinary iodine excretion, 219 [120-471] μg/L) were included in the study (Table 1). While the prevalence of overweight/obesity was 5.4%, the prevalence of underweight was 22.8%. The normal range of TSH was defined as 0.021 to 2.934 mU/L, and the normal range of FT4 was defined as 9.27 to 19.18 pmol/L. Maternal baseline characteristics were compared between the euthyroidism, isolated hypothyroxinemia, and subclinical hypothyroidism groups (Table 2). There were no statistically significant differences in age, BMI, prevalence of overweight/obesity or underweight, or sociodemographic characteristics among the 3 groups. The proportion of smokers was significantly higher in the isolated hypothyroxinemia group. Gestational weeks at the sampling of thyroid function were significantly later in isolated hypothyroxinemia group. The subclinical hypothyroidism group showed the tendency to be diagnosed later than the euthyroidism group without statistical significance. The isolated hypothyroxinemia group showed significantly higher TSH levels and lower FT4 levels than the euthyroidism group. The subclinical hypothyroidism group showed significantly higher TSH levels and lower FT4 levels than the euthyroidism group. The subclinical hypothyroidism group showed a higher prevalence of TPOAb and TgAb positivity than the euthyroidism and isolated hypothyroxinemia groups; however, the difference was not statistically significant. The median iodine status in each group was adequate or above; however, the median level of urinary iodine excretion in the isolated hypothyroxinemia group was comparatively lower than that in the euthyroidism and subclinical hypothyroidism groups.

Table 1. Descriptive statistics of 1105 women

	Value
Maternal age, years	35 (33-38)
BMI, kg/m^2	20.0 (18.6-21.6)
Overweight/obesity, n (%)	60 (5.4)
Underweight, n (%)	252 (22.8)
Nulliparous, n (%)	588 (53.2)
Smokers, n (%)	13 (1.2)
Married, n (%)	1088 (98.5)
Workers, n (%)	611 (55.3)
Educational levels, n (%)	
University or higher	666 (60.3)
High school	369 (33.4)
Junior high school	4 (0.4)
Missing data	66 (6.0)
Annual income, n (%)	
10 million yen or more	361 (32.7)
6-10 million yen	385 (34.8)
Less than 6 million yen	240 (21.7)
Missing data	119 (10.8)
Gestational weeks at the sampling of thyroid function, weeks	10.7 (9.7-11.7)
TSH, mU/L	0.70 (0.30-1.23)
FT4, pmol/L	12.23 (11.07-13.64)
Gestational weeks at the sampling of antithyroid antibodies and urine, weeks	25.0 (24.1-26.4)
TPOAb positivity, n (%)	130 (11.8)
TgAb positivity, n (%)	184 (16.7)
Urinary iodine excretion, μg/L	219 (120-471)
Urinary iodine excretion, μg/gCr	291 (175-672)

Data are median (IQR) or number (percentage).

Perinatal Characteristics

There were no statistically significant differences in birthweight, gestational weeks at birth, proportion of preterm births, prevalence of gestational diabetes mellitus, or hypertensive disorders of pregnancy among the euthyroidism, isolated hypothyroxinemia, and subclinical hypothyroidism groups (Table 3). The proportion of levothyroxine prescriptions was highest in the subclinical hypothyroidism group, and levothyroxine was never prescribed for isolated hypothyroxinemia. Levothyroxine was prescribed by the attending physicians after study enrollment.

Associations of Perinatal Outcomes With Isolated Hypothyroxinemia and Subclinical Hypothyroidism

The prevalence of SGA was significantly higher in the isolated hypothyroxinemia and subclinical hypothyroidism groups than in the euthyroidism group (28.0% and 19.2%, respectively, vs 5.7%; $P < .01$) (Table 4; Fig. 2). In an unadjusted model, isolated hypothyroxinemia (OR 6.48; 95% CI 2.60-16.18) and subclinical hypothyroidism (OR 3.97; 95% CI 1.44-10.93) were associated with a significantly higher risk of SGA compared with euthyroidism (Model 1 in Table 4). After multivariable adjustment, the OR with 95% CI for SGA was 12.51 (4.41-35.53) for isolated hypothyroxinemia and 4.44 (1.57-12.56) for subclinical hypothyroidism, respectively (Model 2 in Table 4).

The prevalence of LGA was similar among the euthyroidism, isolated hypothyroxinemia, and subclinical hypothyroidism groups (11.1%, 12.0%, and 11.5%, respectively; $P = .82$). In the unadjusted and adjusted models, isolated hypothyroxinemia and subclinical hypothyroidism were not associated with LGA compared with euthyroidism (Table 4).

The prevalence of low birth weight tended to be higher in isolated hypothyroxinemia and subclinical hypothyroidism groups than the euthyroidism group (16.0% and 15.4%, respectively, vs 8.4%, $P = .11$). In the unadjusted and adjusted models, isolated hypothyroxinemia and subclinical hypothyroidism were not significantly associated with low birth weight compared with euthyroidism (Table 4).

Five participants in the subclinical hypothyroidism group started to take levothyroxine after study enrollment. The newborns of the participants prescribed levothyroxine were

Table 2. Baseline maternal characteristics of the euthyroidism, isolated hypothyroxinemia, and subclinical hypothyroidism groups (n = 1032)

	Euthyroidism (n = 981)	Isolated hypothyroxinemia (n = 25)	Subclinical hypothyroidism (n = 26)	*P* value
Maternal age, years	35 (33-38)	36 (35-39)	37 (33-39)	.43
BMI, kg/m^2	20.0 (18.6-21.5)	21.1 (18.4-22.3)	20.2 (19.2-21.8)	.58
Overweight/obesity, n (%)	39 (4.0)	2 (8.0)	1 (3.9)	.78
Underweight, n (%)	222 (22.7)	7 (28.0)	5 (19.2)	
Nulliparous, n (%)	521 (53.1)	13 (52.0)	19 (73.1)	.12
Smokers, n (%)	**9 (0.9)**	**3 (12.0)**	**0 (0.0)**	**<.01**
Married, n (%)	964 (99.0)	25 (100.0)	26 (100.0)	1.00
Workers, n (%)	545 (56.4)	19 (76.0)	15 (57.7)	.15
Educational levels, n (%)[a]				.73
University or higher	595 (64.4)	14 (58.3)	18 (72.0)	
High school	326 (35.3)	10 (41.7)	7 (28.0)	
Junior high school	3 (0.3)	0 (0.0)	0 (0.0)	
Annual income, n (%)[b]				.62
10 million yen or more	327 (37.2)	10 (50.0)	8 (34.8)	
6-10 million yen	336 (38.3)	8 (40.0)	9 (39.1)	
Less than 6 million yen	215 (24.5)	2 (10.0)	6 (26.1)	
Gestational weeks at the sampling of thyroid function, weeks	**10.7 (9.7-11.6)**	**12.6 (11.5-13.4)****	**11.7 (10.0-12.3)**	**<.01**
TSH, mU/L	**0.72 (0.37-1.22)**	**0.96 (0.56-2.20)***	**3.69 (3.10-4.42)****	**<.01**
FT4, pmol/L	**12.10 (11.20-13.38)**	**8.88 (8.62-9.14)****	**10.68 (10.10-11.62)****	**<.01**
TPOAb positivity, n (%)	112 (11.4)	2 (8.0)	4 (15.4)	.77
TgAb positivity, n (%)	155 (15.8)	3 (12.0)	8 (30.8)	.11
Urinary iodine excretion, μg/L	225 (122-484)	165 (115-312)	302 (111-843)	.30
Urinary iodine excretion, μg/gCr	295 (180-687)	228 (127-406)	326 (155-996)	.10
Hemoglobin A1c, %	5.2 (5.0-5.3)	5.2 (5.1-5.3)	5.2 (5.1-5.3)	.19
Previous diseases, n (%)				
Diabetes	1 (0.1)	1 (4.0)	0 (0.0)	.09
Hypertension	13 (1.3)	1 (4.0)	0 (0.0)	.43
Anti-phospholipid antibody syndrome	3 (0.3)	0 (0.0)	0 (0.0)	1.00
Chronic kidney disease	5 (0.5)	0 (0.0)	0 (0.0)	1.00

Data are presented as medians (IQR) or numbers (percentages). Bold values indicate significant differences ($P < .05$) in the Kruskal–Wallis test, χ^2 analysis, or Fisher's exact test.
Significant differences in Steel's post hoc test are presented as $*P < .05$ and $**P < .01$ compared with the euthyroidism group.
Abbreviations: FT4, free thyroxine; TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody.
[a,b]The analyzed numbers (n = 974 and 922, respectively) do not correspond to the total due to missing values.

neither SGA, LGA, nor low birth weight. Sensitivity analysis excluding the participants prescribed levothyroxine showed the statistically significant association of subclinical hypothyroidism with SGA but not with LGA and low birth weight (data not shown).

Discussion

This is the first study to show the association between isolated hypothyroxinemia and subclinical hypothyroidism with SGA during the first trimester of pregnancy, focusing on the unique cohort population, a nonobese population with adequate iodine intake.

Small birth size, including SGA and low birth weight, increases the risk for perinatal mortality. Furthermore, small birth size predicts the risk for long-term health, including noncommunicable diseases and neurodevelopmental disorders in adulthood [13-15].

Subclinical hypothyroidism is reported to increase the risk of multiple adverse pregnancy outcomes, including low birth weight and SGA [5, 16]. We found a corresponding effect of subclinical hypothyroidism on fetal birthweight, as previously reported. However, the reported effects of isolated hypothyroxinemia on fetal birthweight are controversial. Su et al reported an increased risk of SGA in isolated hypothyroxinemia [17], and Nazarpour et al reported an increased risk of low birth weight in isolated hypothyroxinemia [18]. However, some reports have shown the association between macrosomia or LGA and isolated hypothyroxinemia [5, 19-21].

There are 2 main reasons for these discrepancies. First is the timing of the thyroid function assessment. After peaking at 10 gestational weeks, the increased FT4 concentrations decrease to a level lower than the FT4 concentrations before pregnancy. The suppressed TSH concentrations recover dynamically. Thus, depending on the timing of the diagnosis, women with different characteristics are categorized as having

Table 3. Perinatal outcomes according to maternal thyroid hormone status in the first trimester

	Euthyroidism (n = 981)	Isolated hypothyroxinemia (n = 25)	Subclinical hypothyroidism (n = 26)	*P* value
Birthweight, g	2998 (2775-3252)	2992 (2648-3348)	2913 (2587-3305)	.73
Macrosomia, n (%)	11 (1.1)	0 (0.0)	0 (0.0)	1.00
Gestational weeks at birth, weeks	39 (38-40)	39 (38-40)	39 (38-40)	.32
Preterm birth, n (%)	47 (4.8)	1 (4.0)	0 (0.0)	.75
Stillbirth, n (%)	0 (0)	0 (0)	0 (0)	1.00
Cesarean sections, n (%)	265 (27.0)	6 (24.0)	6 (23.1)	.86
Apgar score 7 or less				
At 1 minute	**41 (4.2)**	**3 (12.0)**	**3 (11.5)**	**.03**
At 5 minutes	7 (0.7)	0 (0.0)	0 (0.0)	1.00
NICU admission, n (%)	47 (4.8)	2 (8.0)	2 (7.7)	.29
Placental weight, g	530 (470-600)	575 (458-639)	523 (444-557)	.21
Gestational weight gain, kg	10.0 (7.9-12.2)	10.3 (8.1-13.6)	9.1 (7.8-11.8)	.47
Gestational diabetes mellitus, n (%)	29 (3.0)	2 (8.0)	1 (3.9)	.20
Hypertensive disorders of pregnancy, n (%)	25 (2.5)	0 (0.0)	0 (0.0)	1.00
Levothyroxine medication, n (%) [a]	**0 (0.0)**	**0 (0.0)**	**5 (19.2)**	**<.01**

Data are median (IQR) or number (percentage). Bold indicates significant differences ($P < .05$) of Kruskal–Wallis test, χ^2 analysis or Fisher's exact test.
Significant differences of Steel's post hoc test are presented as $^*P < .05$ and $^{**}P < .01$ compared with the euthyroidism group.
Abbreviation: NICU, neonatal intensive care unit.
[a]Women who started levothyroxine medication after the study enrollment were counted.

Table 4. Association of isolated hypothyroxinemia and subclinical hypothyroidism with SGA, LGA, and low birth weight

	Euthyroidism (n = 981)	Isolated hypothyroxinemia n = 25)	Subclinical hypothyroidism (n = 26)
Number (%)			
SGA	56 (5.7)**	7 (28.0)**	5 (19.2)**
LGA	109 (11.1)	3 (12.0)	3 (11.5)
Low birth weight	82 (8.4)	4 (16.0)	4 (15.4)
Model 1 unadjusted			
SGA	Reference	6.48 (2.60-16.18)**	3.97 (1.44-10.93)**
LGA	Reference	1.10 (0.32-3.74)	1.05 (0.31-3.57)
Low birth weight	Reference	2.10 (0.70-6.25)	2.00 (0.67-5.94)
Model 2[a]			
SGA	Reference	12.51 (4.41-35.53)**	4.44 (1.57-12.56)**
LGA	Reference	1.19 (0.33-4.33)	1.12 (0.32-3.96)
Low birth weight	Reference	2.23 (0.64-7.76)	2.19 (0.70-6.83)

Abbreviations: LGA, large for gestational age; SGA, small for gestational age.
[a]Model 2: Multivariable analysis adjusted with maternal age, body mass index, smoking, parity, fetal sex, urinary iodine excretion, antithyroid peroxidase antibody positivity, gestational weight gain, and gestational weeks at the sampling of thyroid function.
**Statistical significance with $P < .01$.

isolated hypothyroxinemia, which leads to different pregnancy outcomes.

Second is the multiple etiologies of isolated hypothyroxinemia, which are difficult to adjust completely. Iodine deficiency is a well-known risk factor for isolated hypothyroxinemia [22, 23]. There is only 1 previous report evaluating maternal urinary iodine concentrations; Nazarpour et al reported that isolated hypothyroxinemia with adequate iodine intake showed a higher risk of low birth weight than euthyroid women [18]. Obesity has also been revealed as a common risk factor for isolated hypothyroxinemia. Advanced peripheral deionization to decrease plasma FT4 levels has been reported in obese individuals [6, 24]. Contrary to our study, 2 Chinese cohorts [20, 21] and a Caucasian cohort from the United States [19] suggested an increased risk of macrosomia in isolated hypothyroxinemia during the first trimester. In these reports, maternal BMI and the prevalence of overweight/obesity were much higher than our study. There may be nonadjustable confounding factors in the obese population that induce fetal overgrowth. For instance, insulin resistance is reported to lower the concentrations of FT4, which can relate maternal isolated hypothyroxinemia to gestational diabetes mellitus or macrosomia [25, 26]. Korevaar et al reported an association between isolated hypothyroxinemia and placental angiogenic

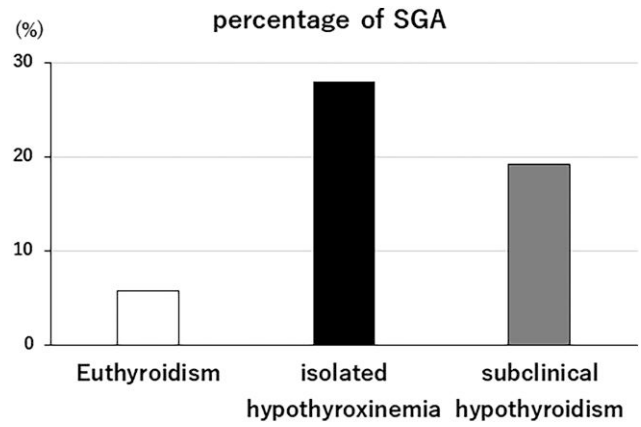

Figure 2. Percentage of SGA according to the thyroid function. $P < .0001$ using Fisher's exact test.

factors, proangiogenic placental growth factor, and antiangiogenic soluble FMS-like tyrosine kinase-1 [27], which could not be verified in our study. Elevated TSH concentrations in subclinical hypothyroidism are reported to be a compensatory reaction for the abnormal thyroidal response to hCG [28]. As for isolated hypothyroxinemia without iodine deficiency and obesity, dysfunction of the hypothalamic–pituitary–thyroid axis could be hypothesized; however, little is known. Smoking is reported to be associated with hypothyroxinemia and unelevated TSH during the first trimester [29]. Although the absolute number was small, the proportion of smoking was significantly higher in the isolated hypothyroxinemia group in our study. Further studies are required to fully understand these effects on pregnancy outcomes.

The main limitation of our study is the limited cohort size. The small sample size of isolated hypothyroxinemia group and subclinical hypothyroidism group may result in the wide 95% CIs in the logistic regression models. Although subclinical hypothyroidism group showed higher rate of thyroid autoimmunity, there was no statistical significance, maybe due to the limited sample size. And although the proportion of low birth weight in isolated hypothyroxinemia group and subclinical hypothyroidism group was almost twice as high as the euthyroidism group, there was no statistical significance. These difficulties in assessing the impact of thyroid autoimmunity and the effect on low birth weight may be due to the limited sample size. The gestational weeks at the sampling of thyroid function were slightly later in the subclinical hypothyroidism group (11.7; 10.0-12.3 weeks) and significantly later in the isolated hypothyroxinemia group (12.6; 11.5-13.4 weeks) compared with the euthyroid group (10.7; 9.7-11.6 weeks). After peaking at 10 gestational weeks, FT4 levels decreased as the effect of hCG is decreased. Thus, the categorization might be affected by the timing of the sampling. We found statistical significance in the association of isolated hypothyroxinemia and subclinical hypothyroidism with SGA after the adjustment for gestational weeks at the sampling; however, further investigation on the appropriate duration of thyroid function test is necessary. Furthermore, this cohort may not represent the general Japanese population, as this is a single-center cohort study. We need to confirm the reproducibility and robustness with a larger population in the future study.

Contrary to the worldwide trend of increasing risk of macrosomia and LGA due to the increase in maternal obesity and diabetes [30], Japan has a unique and serious health problem: maternal thinness, resulting in an increased risk of low birth weight and SGA [31, 32]. Japan was known as an iodine-sufficient area even prior to universal salt iodization [33]. Thus, the Japanese cohort can be regarded as a distinct population that can provide novel insights into maternal thyroid function and fetal birthweight.

In conclusion, isolated hypothyroxinemia and subclinical hypothyroidism in a nonobese population with adequate iodine status are independent risk factors for SGA. Further studies are needed, but screening and careful perinatal checkups for isolated hypothyroxinemia and subclinical hypothyroidism may help identify pregnant women at high risk for SGA.

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Disclosures

N.A. reported receiving speaking fees from Roche Diagnostics K.K., Tokyo. The other authors declare no conflicts of interest.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References

1. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. *Nat Rev Endocrinol*. 2017;13(10):610-622.
2. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. *N Engl J Med*. 1991;324(8):532-536.
3. Dong AC, Stagnaro-Green A. Differences in diagnostic criteria mask the true prevalence of thyroid disease in pregnancy: a systematic review and meta-analysis. *Thyroid*. 2019;29(2):278-289.
4. Korevaar TIM, Derakhshan A, Taylor PN, *et al*. Consortium on thyroid and pregnancy–study group on preterm birth. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: a systematic review and meta-analysis. *JAMA*. 2019;322(7):632-641.
5. Derakhshan A, Peeters RP, Taylor PN, *et al*. Association of maternal thyroid function with birthweight: a systematic review and individual-participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2020;8(6):501-510.
6. Ramezani Tehrani F, Nazarpour S, Behboudi-Gandevani S. Isolated maternal hypothyroxinemia and adverse pregnancy

outcomes: a systematic review. *J Gynecol Obstet Hum Reprod*. 2021;50(7):102057.
7. Ogawa K, Morisaki N, Sago H, Fujiwara T, Horikawa R. Association between women's perceived ideal gestational weight gain during pregnancy and pregnancy outcomes. *Sci Rep*. 2018;8(1):11574.
8. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino Y, Nanjo K, Tajima N, *et al*. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Investig*. 2010;1(5):212-228.
9. Ogihara T, Kikuchi K, Matsuoka H, *et al*.; Japanese Society of Hypertension Committee. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res*. 2009;32(1):3-107.
10. WHO/UNICEF/ICCIDD. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination: a Guide for Programme Managers*. 3rd ed. World Health Organization Press, 2007.
11. Santos S, Voerman E, Amiano P, *et al*. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian cohorts. *BJOG*. 2019;126(8):984-995.
12. Bliddal S, Derakhshan A, *et al*. Association of thyroid peroxidase antibodies and thyroglobulin antibodies with thyroid function in pregnancy: an individual participant data meta-analysis. *Thyroid*. 2022;32(7):828-840.
13. Larroque B, Bertrais S, Czernichow P, Léger J. School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study. *Pediatrics*. 2001;108(1):111-115.
14. Risnes KR, Vatten LJ, Baker JL, *et al*. Birthweight and mortality in adulthood: a systematic review and meta-analysis. *Int J Epidemiol*. 2011;40(3):647-661.
15. Varley BJ, Nasir RF, Skilton MR, Craig ME, Gow ML. Early life determinants of vascular structure in fetuses, infants, children, and adolescents: a systematic review and meta-analysis. *J Pediatr*. 2023;252:101-110.e9.
16. Maraka S, Ospina NM, O'Keeffe DT, *et al*. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. *Thyroid*. 2016;26(4):580-590.
17. Su PY, Huang K, Hao JH, *et al*. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *J Clin Endocrinol Metab*. 2011;96(10):3234-3241.
18. Nazarpour S, Ramezani Tehrani F, Rahmati M, Amiri M, Azizi F. Effects of isolated maternal hypothyroxinemia on adverse pregnancy outcomes. *Arch Gynecol Obstet*. 2022;305(4):903-911.
19. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, *et al*. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol*. 2008;112(1):85-92.
20. Gong X, Liu A, Li Y, *et al*. The impact of isolated maternal hypothyroxinemia during the first and second trimester of gestation on pregnancy outcomes: an intervention and prospective cohort study in China. *J Endocrinol Invest*. 2019;42(5):599-607.
21. Liu Y, Guo F, Zhou Y, Yang X, Zhang Y, Fan J. The interactive effect of prepregnancy overweight/obesity and isolated maternal hypothyroxinemia on macrosomia. *J Clin Endocrinol Metab*. 2021;106(7):e2639-e2646.
22. Glinoer D, de Nayer P, Bourdoux P, *et al*. Regulation of maternal thyroid during pregnancy. *J Clin Endocrinol Metab*. 1990;71(2):276-287.
23. Glinoer D, Delange F, Laboureur I, *et al*. Maternal and neonatal thyroid function at birth in an area of marginally low iodine intake. *J Clin Endocrinol Metab*. 1992;75(3):800-805.
24. Dosiou C, Medici M. Management of endocrine disease: isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns. *Eur J Endocrinol*. 2017;176(1):R21-R38.
25. Bassols J, Prats-Puig A, Soriano-Rodríguez P, *et al*. Lower free thyroxin associates with a less favorable metabolic phenotype in healthy pregnant women. *J Clin Endocrinol Metab*. 2011;96(12):3717-3723.
26. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *J Clin Endocrinol Metab*. 2007;92(2):491-496.
27. Korevaar TI, Steegers EA, de Rijke YB, *et al*. Placental angiogenic factors are associated with maternal thyroid function and modify hCG-mediated FT4 stimulation. *J Clin Endocrinol Metab*. 2015;100(10):E1328-E1334.
28. Korevaar TI, de Rijke YB, Chaker L, *et al*. Stimulation of thyroid function by human chorionic gonadotropin during pregnancy: a risk factor for thyroid disease and a mechanism for known risk factors. *Thyroid*. 2017;27(3):440-450.
29. Männistö T, Hartikainen AL, Vääräsmäki M, *et al*. Smoking and early pregnancy thyroid hormone and anti-thyroid antibody levels in euthyroid mothers of the Northern Finland Birth Cohort 1986. *Thyroid*. 2012;22(9):944-950.
30. Henriksen T. The macrosomic fetus: a challenge in current obstetrics. *Acta Obstet Gynecol Scand*. 2008;87(2):134-145.
31. Enomoto K, Aoki S, Toma R, Fujiwara K, Sakamaki K, Hirahara F. Pregnancy outcomes based on pre-pregnancy body mass index in Japanese women. *PLoS One*. 2016;11(6):e0157081.
32. Normile D. Staying slim during pregnancy carries a price. *Science*. 2018;361(6401):440.
33. Fuse Y, Ohashi T, Yamaguchi S, Yamaguchi M, Shishiba Y, Irie M. Iodine status of pregnant and postpartum Japanese women: effect of iodine intake on maternal and neonatal thyroid function in an iodine-sufficient area. *J Clin Endocrinol Metab*. 2011;96(12):3846-3854.