Mother’s iodine exposure and infants’ hypothyroidism: the Japan environment and children’s study

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Abstract. In this study, we aimed to determine the association of neonatal/post-neonatal hypothyroidism with mother’s iodine exposure, especially povidone iodine disinfection, and hysterosalpingography. Participants were mother–child pairs in a Japanese birth cohort (n = 100,286). Risk factors of hypothyroidism were supplement intake, seaweed intake, other daily iodine intake, povidone iodine disinfection at delivery, and maternal history of hysterosalpingography, thyroid disease (Graves’ disease and Hashimoto’s thyroiditis), and medication (thiamazole and levothyroxine). Congenital hypothyroidism (CH) at age 1 year was assessed using a questionnaire. Transient hypothyroidism was defined as elevated thyroid stimulating hormone level at birth and absence of CH at age 1 year. The incidence of CH at age 1 year per 100 children was 1.1 for those born at 22–30 weeks’ gestation, 0.17 following povidone iodine disinfection, and 0.07, 0.95, 0.81, 1.17, and 1.15 with a maternal history of hysterosalpingography, Graves’ disease, Hashimoto’s thyroiditis, thiamazole use, and levothyroxine use, respectively. Odds ratios (95% confidence intervals) of CH at age 1 year for povidone iodine disinfection, hysterosalpingography history, maternal Graves’ disease, and maternal Hashimoto’s thyroiditis were 1.13 (0.71–1.79), 0.47 (0.07–3.36), 7.06 (3.70–13.5), and 5.93 (2.90–12.1), respectively. For transient hypothyroidism for povidone iodine disinfection and hysterosalpingography history, these values were 1.99 (1.51–2.62) and 0.63 (0.20–1.96), respectively. Maternal thyroid disease greatly increased neonatal/post-neonatal hypothyroidism risk. Povidone iodine disinfection may increase transient hypothyroidism risk but not the risk at 1 year of age. Hysterosalpingography does not increase hypothyroidism risk from birth to age 1 year.

Key words: Congenital hypothyroidism, Cretinism, Povidone iodine disinfection, Hysterosalpingography, Chromatography-tandem mass spectrometry screening

CONGENITAL HYPOTHYROIDISM (CH) is a thyroid hormone deficiency syndrome in newborns that is caused by incomplete thyroid development and decreased thyroid hormone biosynthesis or thyroid-stimulating hormone (TSH) secretion [1]. This disease was long thought to occur in approximately 1 in 3,000 to 4,000 newborns [2, 3]. In Japan, where newborn mass screening is routinely performed [4], a 2014 study estimated that CH occurred in 1 in 4,000 newborns [5]. Recent evidence suggests that the incidence may be 1 in 2,000 to 1 in 4,000 [5, 6]. In Italy, using the cutoff value of 10 μIU/mL for TSH, a previous study reported a CH incidence of 1 in 1,154 [7]. Incidence estimates have increased, possibly because clinicians have recognized that CH is a more common condition than was previously thought and have worked to diagnose and actively treat CH. Epidemiological investigations are necessary to determine whether there are other reasons for this phenomenon.

Hypothyroidism in the neonatal and post-neonatal periods occurs via many mechanisms. The causes of CH are broadly classified as primary (disorder of the thyroid gland), central (disorder of the hypothalamus or pituitary gland), or peripheral (impaired thyroid hormone action). Mutations of the Pax8 and Nkx2-1 genes are associated with a subset of permanent primary CH that results in thyroid dysplasia [8]. Mutations of the TG, TPO, and DUOX2 genes have also been detected in a subset of newborns with decreased thyroid hormone biosynthesis [9, 10]. In contrast, most cases of incomplete thyroid development are still thought to be sporadic [11]. The environmental etiology of CH needs to be further investigated.

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The environmental factors previously found to be associated with permanent CH are female sex, pre- and post-term delivery, and twin pregnancy (incidence of 1 in 900) [10, 12]. Some cases of transient hypothyroidism may be attributed to transplacental migration of antithyroid agents, TSH receptor-blocking antibodies [13], and maternal excess intake of iodine. Because thiamazole, an antithyroid agent, is transferred to the fetus via the placenta [14], use of this medication by the mother can be expected to be associated with offspring hypothyroidism. However, the incidence of hypothyroidism in the children of women using such agents is not well known.

Mothers may also be exposed to iodine from other sources, such as supplements [15], the consumption of seaweed (a traditional Japanese food) [16], disinfection with povidone iodine at delivery [13], and hysterosalpingography used as a fertility treatment to flush the ovarian tubes and increase the chance of pregnancy [17]. Clinicians may have recently refrained from using povidone iodine disinfection for fear of increasing the hypothyroidism risk, but it is unknown whether this type of disinfection has adverse effects. At present, hysterosalpingography with oil-soluble contrast agent could be a risk factor of neonatal hypothyroidism [18]; hysterosalpingography with water-soluble contrast agent is considered to be safer. Recent data regarding the influence of hysterosalpingography on hypothyroidism risk are needed.

Among children aged ≤3 years, a subset of patients treated for CH are later determined not to have permanent CH at the end of the treatment. In the present study, we used birth cohort data that included CH history and test results using dried blood spot samples on chromatography paper [19]. We aimed to quantify the associations between varied routes of mother’s iodine exposure and child hypothyroidism incidence from birth to 1 year of age. We calculated the incidence rates and odds ratios (ORs) for these associations in the Japanese population [20-23].

Materials and Methods

Enrollment

Details of the Japan Environment and Children’s Study (JECS) have been published elsewhere [20]. In brief, the cohort study, recruiting from 2011 to 2014, followed over 100,000 children born in 15 regions across Japan from preconception to puberty [24]. We used the following JECS data files: “jecs-ta-20190930-qsn,” “jecs-ta-20200331-tsh of jecs-ta-20190930,” and “jecs-an-20180131.”

Exposure and outcome variables

Data on exposure to disinfection with povidone iodine at delivery and maternal history of hysterosalpingography were gathered using an obstetrician questionnaire. Because indicating whether disinfection was conducted at delivery was voluntary, the number of cases was reduced to nearly half the original number of participants. Hysterosalpingography within 3 months before pregnancy was assessed. Mother’s iodine exposure in the first and second or third trimesters comprised the following routes: supplement intake, seaweed intake three or more times per week, and estimated insufficient or excessive iodine intake. A self-administered food frequency questionnaire [25] was used to estimate the amount of iodine intake through consumption of supplements and seaweed. We considered an estimated iodine intake of 2,000 μg/day to be excessive exposure for pregnant women, referring to the 2015 and 2020 Dietary Reference Intakes for Japan [26]. Data on thyroid disease (Graves’ disease and Hashimoto’s thyroiditis) and medication for thyroid disease (thiamazole and levothyroxine) were collected using questions asked of mothers during the first trimester of pregnancy. Gestational age at birth was categorized as 22–30 weeks, 31–36 weeks, 37–41 weeks, or ≥42 weeks because the fetal serum T<sub>3</sub> concentration in the fetal thyroid gland gradually increases from 30 weeks of gestation [27].

We sent the JECS questionnaire by mail to caregivers when their children were aged 1 year, asking whether a physician had diagnosed the child with hypothyroidism or cretinism. We also collected whole blood spot samples on chromatography paper from the children’s heel at the age of 4–6 days. TSH concentration was examined using this blood sample in semi-quantitative immunofluorescent assay analysis with an AutoDELFIA (PerkinElmer Inc., Waltham, MA, USA). We restricted the analysis to children sampled between 4 and 6 days of age. There is no global criterion for TSH level at birth to screen for CH. Following the Japanese guidelines for pediatricians [5], we set the criterion for TSH to ≥10 μIU/mL in blood spot samples. In this study, we defined “transient hypothyroidism” as having serum TSH levels ≥10 μIU/mL at birth but subsequently not being identified as having CH on the caregiver questionnaire.

Sensitivity analysis

We calculated the incidence of TSH ≥10 μIU/mL among infants born at 37–41 weeks’ gestation (term delivery). This analysis was intended to identify risk factors after excluding for the influence of the decreased surge in TSH levels at birth among early-term neonates.

Among the 18 Japanese prefectures in this study, 16 have a coastline. For the two inland prefectures, a subset...
of women might have lower iodine intake. In another sensitivity analysis, we constructed tables of incidence and ORs of a diagnosis of CH or cretinism according to the questionnaire, and restricted the analysis to data from these two inland prefectures. In a third sensitivity analysis, we calculated the incidence and ORs of a diagnosis of CH or cretinism according to the questionnaire and restricted the analysis to data from mothers aged 35 years or more. In this analysis, we aimed to explore whether the results may differ with older childbearing age.

**Statistical analysis**

We calculated the incidence of CH (both determined by blood spot samples and as reported on the caregiver questionnaires) for each examined route of mother’s iodine exposure. We also computed ORs and 95% confidence intervals to assess the effects of the exposures on the outcomes. Furthermore, we calculated the ORs of transient hypothyroidism. We conducted all statistical analyses using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA). p-values were two-sided, and p < 0.05 was considered to indicate a significant difference.

The JECS protocol was reviewed and approved by the Ministry of the Environment’s Institutional Review Board on Epidemiological Studies and the ethics committees of all participating institutions. The study was conducted in accordance with the ethical guidelines and regulations outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

**Results**

We analyzed data on 100,286 children (female, 48.8%) at baseline. Table 1 shows numbers and percentages of mothers who had different levels of iodine exposure. A total 0.14% of cases had questionnaire-reported child CH at the age of 1 year, 0.7% had TSH values ≥10 μIU/mL in blood spot samples, and 0.6% had transient hypothyroidism. The percentages of mothers with an estimated iodine intake of >2,000 μg/day in the first trimester, the second to third trimester, and throughout the pregnancy were 0.23%, 0.24%, and 0.02%, respectively. In total, 29.9% of mothers had povidone iodine disinfection at delivery, 1.7% had a history of hysterosalpingography, 1.1% had Graves’ disease, and 1.0% had Hashimoto’s thyroiditis.

Table 2 shows the incidence rate of CH, as measured using the questionnaire. The CH incidence was 0.15% and 0.14% in male and female infants, respectively. The incidence was relatively high for children born at 22–30 weeks (1.1%) and 31–36 weeks (0.18%) of gestation. Twins did not have higher incidence of CH (0.11%).

Among the examined routes of iodine exposure, a relatively high incidence of CH was found in cases where the mother had an iodine intake of >2,000 μg/day in early pregnancy (0.67%), Graves’ disease (0.95%), Hashimoto’s thyroiditis (0.81%), and a history of taking thiamazole (1.17%) or levothyroxine (1.15%).

Table 3 shows the ORs of CH, as measured using the questionnaire, for the factors of interest. The ORs were significantly higher for infants born at 22–30 weeks’ gestation (OR = 8.23) compared with those born at 37–41 weeks’ gestation. The ORs were significantly higher in cases involving maternal Graves’ disease (OR = 7.06), Hashimoto’s thyroiditis (OR = 5.93), thiamazole use (OR = 8.52), and levothyroxine use (OR = 8.55). Disinfection with povidone iodine (OR = 1.13) and history of hysterosalpingography (OR = 0.47) were not statistically associated with the outcome.

Table 4 shows the ORs of CH, defined as TSH values ≥10 μIU/mL in blood spot samples. The ORs were significantly lower for infants born at 31–36 weeks’ gestation (OR = 0.44) compared with those born at 37–41 weeks’ gestation. The ORs were significantly higher in cases where mothers had an iodine intake of <75 μg/day throughout their pregnancy (OR = 1.32), disinfection with povidone iodine at delivery (OR = 1.97), Graves’ disease (OR = 4.04), thiamazole use (OR = 6.19), and levothyroxine use (OR = 2.98). A history of hysterosalpingography was not statistically associated with the outcome of TSH values ≥10 μIU/mL (OR = 0.57).

Table 5 shows the ORs of transient hypothyroidism, as defined above. The ORs were significantly higher in cases where mothers had an iodine intake of <75 μg/day throughout their pregnancy (OR = 1.50), disinfection with povidone iodine at delivery (OR = 1.99), Graves’ disease (OR = 4.16), thiamazole use (OR = 6.85), and levothyroxine use (OR = 2.98). A history of hysterosalpingography was not statistically associated with the outcome of transient CH (OR = 0.63).

In the first sensitivity analysis (Supplementary Table 1), 444 cases with TSH values ≥10 μIU/mL were found among 56,251 neonates born at term gestation (0.79%). The percentages with TSH values ≥10 μIU/mL were 0.73% for male infants, 0.69% for female infants, 0.69% for infants whose mothers consumed seaweed ≥3 times per week, 0.88% for those whose mothers had an iodine intake of <75 μg/day during pregnancy, 1.1% in cases involving disinfection with povidone iodine, 0.43% for cases with a maternal history of hysterosalpingography, 2.8% in cases involving maternal Grave’s disease, 0.81% in cases involving maternal Hashimoto disease, 4.3% in cases with maternal thiamazole use, and 2.2% in cases with maternal levothyroxine use.

In the second sensitivity analysis (Supplementary
Tables 2 and 3), there were significantly increased ORs of hypothyroidism at age 1 year for gestational age 22 to 30 weeks and 31 to 36 weeks, twin birth, maternal Graves’ disease, and maternal thiamazole and levothyroxine use. We found significantly decreased ORs for gestational age 42 weeks or more, estimated iodine intake >2,000 μg/day in the first trimester, and history of hysterosalpingography. The results of the third sensitivity analysis for mothers aged 35 years or more at delivery (Supplementary Tables 4 and 5) did not differ substantially from the main results in Tables 2 and 3.

Discussion

Principal findings

We found no statistically significant associations with caregiver-reported CH in children at 1 year of age for sex, twin birth, excessive or insufficient intake of iodine, disinfection with povidone iodine at delivery, or history of hysterosalpingography (Table 3). Birth at 22–30 weeks of gestation, as well as maternal Graves’ disease and Hashimoto’s thyroiditis and the use of medications for these diseases were identified as risk factors for CH. Post-term birth was identified as a preventive factor. For CH defined as TSH value ≥10 μIU/mL at 4–6 days of age, insufficient iodine intake, povidone iodine disinfection, maternal Graves’ disease, and use of thiamazole and levothyroxine were found to be risk factors (Table 4). Birth at 31–36 weeks of gestation was associated with a lower risk of hypothyroidism, and a history of hysterosalpingography was not demonstrated to be a risk factor. Povidone iodine disinfection, maternal Graves’ disease, and thiamazole and levothyroxine use were found to increase the risk of transient hypothyroidism (Table 5).
although the number of cases with iodine disinfection data was relatively small. History of hysterosalpingography was not identified as a risk factor.

**Comparison with previous research**

According to the data, CH incidence at 1 year of age was 0.14%, indicating that 1 in 696 children were affected. This figure is surprising in comparison with the results of mass screening of 1 CH case in 3461 newborns in Kanagawa Prefecture, Japan from 1979 to 2006 [28]. Japanese prefectures determine their own cutoff values for mass screening. Kanagawa has adopted the TSH cut-off value 9.4 μIU/mL, and most institutions in the prefecture simultaneously assess the free T4 level, which should lower the CH incidence. The measured incidence of CH should be lower at 1 year of age than that at birth because the latter estimate also includes cases of transient hypothyroidism. A report published by Japan’s Ministry of Health, Labour and Welfare estimated the incidence of CH to be 1 in 1700–1900 newborns, using mass-screening data from 2009 to 2014 [29]. In the present survey, we used reports from caregivers rather than physicians. We believe that as participants in a study with a long follow-up period [30], caregivers responded accurately to the survey and rarely misclassified their children as having CH. Indeed, a previous study indicated that the incidence of CH in Japanese neonates has risen over the past two decades [29], and a rising international trend has also been identified [6].

This increase in the incidence of CH may be partly attributable to an increase in preterm births and late childbearing [12]. The results presented in Table 2 support this hypothesis. Generally, the incidence of CH is higher in Asian children than in White and African children [31]. Existing evidence is mixed regarding whether Japanese people consume very high amounts of iodine in the traditional Japanese diet [32, 33]. Our findings suggested that most pregnant women did not consume excessive amounts of iodine (Table 2). We consider it likely that the finding of a high incidence of CH among 1-year-old children is caused by prophylactic thyroid hormone therapy for infants, as has been suggested in a

| Table 2 | Incidence rate of child congenital hypothyroidism (reported on questionnaire at 1 year of age) according to mother/child characteristics, including mother’s iodine exposure |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Mother/child characteristic** | **Incidence per 100 children** |
| **Children’s variables** | |
| Male sex | 77/51,396 (0.15) |
| Female sex | 67/48,890 (0.14) |
| Born at 22–30 weeks’ gestation | 6/541 (1.1) |
| Born at 31–36 weeks’ gestation | 9/5,042 (0.18) |
| Born at 37–41 weeks’ gestation | 128/94,191 (0.14) |
| Born at ≥42 weeks’ gestation | 0/227 (0) |
| Singleton birth | 142,98,395 (0.14) |
| Twin birth | 2/1,847 (0.11) |
| **Mothers’ variables** | |
| Iodine supplement intake | 0/8 (0) |
| Seaweed intake ≥3 times per week | 115/77,868 (0.15) |
| Estimated iodine intake <75 μg/day in the 1st trimester | 53/33,314 (0.16) |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 44/33,024 (0.13) |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 28/20,187 (0.14) |
| Estimated iodine intake >2,000 μg/day in the 1st trimester | 1/149 (0.67) |
| Estimated iodine intake >2,000 μg/day in the 2nd to 3rd trimester | 0/155 (0) |
| Estimated iodine intake >2,000 μg/day in the 1st to 3rd trimester | 0/12 (0) |
| Disinfection with povidone iodine at delivery | 27/16,324 (0.17) |
| History of hysterosalpingography | 1/4,154 (0.07) |
| Thyroid disease | |
| Graves’ disease | 10/1,055 (0.95) |
| Hypothyroidism or Hashimoto’s thyroiditis | 8/988 (0.81) |
| Medication for thyroid disease | |
| Thiamazole | 5/426 (1.17) |
| Levothyroxine | 9/784 (1.15) |
previous study [34]. Although more information on the incidence of permanent CH is required in the field of endocrinology, our risk factor analysis separating out transient hypothyroidism has the potential to contribute to clinical practice.

**High TSH value in the neonatal period**

In our semi-quantitative analysis of blood samples from neonates, insufficient maternal iodine intake was associated with a higher risk of children having TSH values ≥10 μIU/mL (Table 4). This finding is in line with the results of a study conducted among people living in iodine-deficient areas, where maternal hypothyroxinemia and neonatal hypothyroidism are particularly common [27]. Our finding that 20% to 33% of mothers had an iodine intake of <75 μg/day seems to be very large. Although this finding may suggest a limitation of brief-type self-administered diet history questionnaires, it should also be noted that in recent years, Japanese women may have developed an especially high risk of insufficient iodine consumption.

It should be noted that the percentage of neonates born at term gestation with TSH ≥10 μIU/mL (male 0.73%, female 0.69%; Supplementary Table 1) was higher than the percentage with CH at 1 year of age (0.14%, Table 1). Most of the 444 neonates with term births did not appear to be influenced by maternal thyroid disease, as there were only 16 cases involving maternal Grave’s disease and only four cases involving maternal Hashimoto’s disease. The high percentages suggest that detection of CH in mass screening may be more common than thought by clinicians, even among neonates born at term gestation. These results indicate that mass screening has benefitted a substantial number of neonates delivered at term by enabling early intervention with thyroid hormone therapy.

**Implications for clinicians and parents**

Globally, the main causes of transient hypothyroidism are iodine intake deficiency and preterm birth [35]. Other causes may include hysterosalpingography, excessive intake of iodine because of regular consumption of sea-

### Table 3  Odds ratios of child congenital hypothyroidism (reported on questionnaire at 1 year of age) according to mother/child characteristics, including mother’s iodine exposure

| Mother/child characteristic | Odds ratio (95% confidence interval) |
|----------------------------|-------------------------------------|
| **Children’s variables**   |                                     |
| Male (vs. female) sex       | 1.09 (0.79–1.52)                    |
| Born at 22–30 weeks (vs. 37–41 weeks of gestation) | 8.23 (3.61–18.7) |
| Born at 31–36 weeks (vs. 37–41 weeks of gestation) | 1.31 (0.67–2.59) |
| Born at ≥42 weeks (vs. 37–41 weeks of gestation) | 0.998 (0.997–0.998) |
| Twin birth (vs. singleton birth) | 1.33 (0.33–5.39) |
| **Mothers’ variables**      |                                     |
| Iodine supplement intake    | —†                                 |
| Seaweed intake ≥3 times per week | 1.14 (0.76–1.72) |
| Estimated iodine intake <75 μg/day in the 1st trimester | 1.17 (0.83–1.65) |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 0.89 (0.62–1.27) |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 0.95 (0.63–1.44) |
| Estimated iodine intake ≥2,000 μg/day in the 1st trimester | 4.97 (0.69–35.9) |
| Estimated iodine intake ≥2,000 μg/day in the 2nd to 3rd trimester | —† |
| Estimated iodine intake ≥2,000 μg/day in the 1st to 3rd trimester | —† |
| Disinfection with povidone iodine at delivery | 1.13 (0.71–1.79) |
| History of hysterosalpingography | 0.47 (0.07–3.36) |
| Thyroid disease             |                                     |
| Graves’ disease             | 7.06 (3.70–13.5)                    |
| Hypothyroidism or Hashimoto’s thyroiditis | 5.93 (2.90–12.1) |
| Medication for thyroid disease |                                     |
| Thiamazole                  | 8.52 (3.47–20.9)                    |
| Levothyroxine               | 8.55 (4.34–16.8)                    |

† Owing to a small number of cases of child congenital hypothyroidism, this odds ratio could not be calculated.
weed, iodine supplement intake, and transplacental migration of antithyroid medicines and TSH receptor-blocking antibodies [35]. Table 5 shows that only povidone iodine disinfection at delivery and maternal thyroid diseases were risk factors for transient CH; a history of hysterosalpingography was not identified as a risk factor. Clinicians may have concerns regarding the possible adverse effects of povidone iodine disinfection. Table 3 indicates no significant association between the risk of CH at 1 year of age and povidone iodine disinfection, suggesting that if there is any risk linked to povidone iodine disinfection, it is transient (Table 5).

Parents sometimes use hysterosalpingography to assess uterine function and to increase the chances of pregnancy, treating the exam itself as a fertility treatment. Lipid- and water-soluble iodine contrast agents are used for radiography. Lipid-soluble contrast media may be preferred to increase the chances of pregnancy [17]. However, because of concerns that lipid-soluble agents remain in the ovarian tubes for a long time [18], water-soluble contrast agents have recently begun to be used in radiographic examination [36]. In the present study, the agent type was not investigated. Parents may be concerned about the risk of transient hypothyroidism; however, the data in Tables 3–5 suggest that hysterosalpingography does not pose this risk. The reason may be owing to clinicians’ efforts to shift from lipid-soluble to water-soluble agents and to encourage patients to wait several days after the examination before trying for pregnancy.

**Limitations**

This study has several limitations. First, although permanent CH is determined at around 3 years of age, we explored the risk factors for CH at birth and at 1 year of age. A definition of CH using a screening test for TSH during the neonatal period would lead to overdiagnosis of hypothyroidism. Additionally, although levothyroxine Na (L-T₄) would be used for children with CH, use of this agent was not measured at 1 year of age in this

| Table 4 | Odds ratios of child hypothyroidism (TSH ≥10 μIU/mL in blood spot samples) according to mother/child characteristics, including mother’s iodine exposure |
|---------|---------------------------------------------------------------------------------------------------------------|
| **Children’s variables** |                                                                                                               |
| Male (vs. female) sex | 1.08 (0.88, 1.32) |
| Born at 22–30 weeks (vs. 37–41 weeks of gestation) | —† |
| Born at 31–36 weeks (vs. 37–41 weeks of gestation) | 0.44 (0.20, 0.99) |
| Born at ≥42 weeks (vs. 37–41 weeks of gestation) | —† |
| Twin birth (vs. singleton birth) | —† |
| **Mothers’ variables** |                                                                                                               |
| Iodine supplement intake | —† |
| Seaweed intake ≥3 times per week | 0.87 (0.69, 1.09) |
| Estimated iodine intake <75 μg/day in the 1st trimester | 1.22 (0.99, 1.50) |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 1.39 (1.13, 1.70) |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 1.32 (1.05, 1.66) |
| Estimated iodine intake ≥2,000 μg/day in the 1st trimester | —† |
| Estimated iodine intake ≥2,000 μg/day in the 2nd to 3rd trimester | 2.15 (0.30, 15.5) |
| Estimated iodine intake ≥2,000 μg/day in the 1st to 3rd trimester | —† |
| Disinfection with povidone iodine at delivery | 1.97 (1.51, 2.56) |
| History of hysterosalpingography | 0.57 (0.18, 1.79) |
| Thyroid disease |                                                                                                               |
| Graves’ disease | 4.04 (2.40, 6.82) |
| Hypothyroidism or Hashimoto’s thyroiditis | 1.13 (0.42, 3.04) |
| Medication for thyroid disease |                                                                                                               |
| Thiamazole | 6.19 (3.16, 12.2) |
| Levothyroxine | 3.10 (1.53, 6.30) |

† Owing to a small number of cases of child congenital hypothyroidism, this odds ratio could not be calculated.

TSH, thyroid-stimulating hormone.
study. Second, we could not use maternal thyroid hormone or TSH levels as an exposure to determine the influence of maternal thyroid gland function. The range of maternal hormone levels associated with the lowest likelihood of hypothyroidism in neonates may be a question to answer in clinical practice. Third, the diagnoses of maternal thyroid diseases and child CH at 1 year of age were according to questionnaire items on the history of physician diagnosis. Use of medical records for these conditions would be ideal. In this study, child CH at 1 year of age may include acquired hypothyroidism and transient hypothyroidism.

Fourth, because differences in the TSH surge at birth result in a relatively low level of TSH in neonates delivered prematurely, and TSH mass screenings are conducted several times for low-weight infants, the significantly lower odds of TSH ≥10 μIU/mL among neonates born at 31–36 weeks of gestation may be underestimated. Fifth, the details of disinfection with povidone iodine were not recorded. These procedures could include disinfection with vaginal or cesarean birth or omphalotomy. The risk of each type of disinfection could not be evaluated. Sixth, questionnaire-based estimation of iodine intake may be limited; as mentioned above, the proportion of women with insufficient iodine intake was very large. The amount of iodine intake assessed using food frequency questionnaires has been reported to differ substantially from the actual intake [25]. Japanese people often consume iodine in seaweed broth, and this proportion may be overestimated. Seventh, the data on povidone iodine disinfection at delivery may be biased because of the self-report nature of the questionnaire. The proportion of women with disinfection at delivery in Japan can be expected to be larger than that found in the present study. Eighth, the question regarding hysterosalpingography history was restricted to within 3 months before pregnancy.

Table 5  Odds ratios of transient hypothyroidism (TSH ≥10 μIU/mL in blood spot samples; no questionnaire report of congenital hypothyroidism at 1 year of age) according to mother/child characteristics, including mother’s iodine exposure

| Mother/child characteristic | Odds ratio (95% confidence interval) |
|-----------------------------|-------------------------------------|
| **Children’s variables**    |                                     |
| Male (vs. female) sex       | 1.07 (0.87, 1.32)                   |
| Born at 22–30 weeks (vs. 37–41 weeks of gestation) | —† |
| Born at 31–36 weeks (vs. 37–41 weeks of gestation) | 0.49 (0.22, 1.09) |
| Born at ≥42 weeks (vs. 37–41 weeks of gestation) | —† |
| Twin birth (vs. singleton birth) | —† |
| **Mothers’ variables**      |                                     |
| Iodine supplement intake    | —†                                 |
| Seaweed intake ≥3 times per week | 0.84 (0.66, 1.07) |
| Estimated iodine intake <75 μg/day in the 1st trimester | 1.20 (0.97, 1.49) |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 1.40 (1.14, 1.74) |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 1.30 (1.03, 1.66) |
| Estimated iodine intake ≥2,000 μg/day in the 1st trimester | —† |
| Estimated iodine intake ≥2,000 μg/day in the 2nd to 3rd trimester | 2.38 (0.33, 17.2) |
| Estimated iodine intake ≥2,000 μg/day in the 1st to 3rd trimester | —† |
| Disinfection with povidone iodine at delivery | 1.99 (1.51, 2.62) |
| History of hysterosalpingography | 0.63 (0.20, 1.96) |
| Thyroid disease             |                                     |
| Graves’ disease             | 4.16 (2.42, 7.14)                   |
| Hypothyroidism or Hashimoto’s thyroiditis | 0.93 (0.30, 2.91) |
| Medication for thyroid disease |                                     |
| Thiamazole                  | 6.85 (3.48, 13.5)                   |
| Levothyroxine               | 2.98 (1.40, 6.35)                   |

† Owing to a small number of cases of child congenital hypothyroidism, this odds ratio could not be calculated.

TSH, thyroid-stimulating hormone.
Conclusion

Our analysis of a large Japanese birth cohort dataset suggests that maternal thyroid disease increases the risk of CH. Disinfection with povidone iodine at delivery may increase transient hypothyroidism but not CH risk at 1 year of age, although disinfection data were only collected from a subset of participants. Hysterosalpingography does not increase the risk of transient hypothyroidism and or CH at 1 year of age.

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Supplementary Table 1  Incidence rate of child congenital hypothyroidism (TSH ≥10 μIU/mL in blood spot samples) according to maternal iodine exposure

| Characteristics/Iodine exposure route | Incidence per 100 children |
|--------------------------------------|---------------------------|
| Male sex                             | 200/27,375 (0.73)         |
| Female sex                           | 183/26,572 (0.69)         |
| Singleton                            | 444/56,235 (0.79)         |
| Twins                                | 0/16 (0)                  |
| Supplement intake                    | 0/5 (0)                   |
| Seaweed intake 3 times per week or more | 289/41,886 (0.69)     |
| Estimated iodine intake <75 μg/day in the 1st trimester | 143/17,894 (0.80)         |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 153/18,010 (0.88)         |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimesters | 97/11,010 (0.88)          |
| Estimated iodine intake >2,000 μg/day in the 1st trimester | 0/86 (0)                   |
| Estimated iodine intake >2,000 μg/day in the 2nd to 3rd trimester | 0/73 (0)                   |
| Estimated iodine intake >2,000 μg/day in the 1st to 3rd trimester | 0/9 (0)                    |
| Disinfection by povidone iodine at delivery | 102/9,114 (1.1)          |
| History of hysterosalpingography     | 3/698 (0.43)              |
| Maternal thyroid disease             |                           |
| Graves’ disease                      | 15/539 (2.8)              |
| Hypothyroidism or Hashimoto’s thyroiditis | 4/494 (0.81)            |
| Medication for thyroid disease       |                           |
| Thiamazole                           | 9/212 (4.3)               |
| Levothyroxine                        | 8/365 (2.2)               |

Data limited to term delivery.
TSH, thyroid-stimulating hormone.
Supplementary Table 2  Incidence rate of child congenital hypothyroidism (reported on questionnaire at 1 year of age) with inland birthplace location

| Iodine exposure route | Incidence per 100 children |
|----------------------|---------------------------|
| **Inland area**      |                           |
| **Children’s variables** |                 |
| Male sex             | 6/3,602 (0.17)            |
| Female sex           | 12/3,567 (0.34)           |
| Born at 22–30 weeks’ gestation | 3/37 (8.1)              |
| Born at 31–36 weeks’ gestation | 4/350 (1.1)             |
| Born at 37–41 weeks’ gestation | 11/6,762 (0.16)        |
| Born at ≥42 weeks’ gestation | 0/11 (0)                |
| Singleton birth      | 16/7,042 (0.23)           |
| Twin birth           | 2/127 (1.6)              |

**Mothers’ variables**

| Iodine supplement intake | 0/1 (0) |
| Seaweed intake ≥3 times per week | 16/5,738 (0.28) |
| Estimated iodine intake <75 μg/day in the 1st trimester | 5/2,348 (0.21) |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 3/2,395 (0.13) |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 1/1,462 (0.07) |
| Estimated iodine intake >2,000 μg/day in the 1st trimester | 0/11 (0) |
| Estimated iodine intake >2,000 μg/day in the 2nd to 3rd trimester | 0/4 (0) |
| Estimated iodine intake >2,000 μg/day in the 1st to 3rd trimester | 0/0 |
| Disinfection with povidone iodine at delivery | 3/2,161 (0.14) |
| History of hysterosalpingography | 0/67 (0) |
| Thyroid disease | 3/69 (4.4) |
| Graves’ disease | 1/61 (1.6) |
| Hypothyroidism or Hashimoto’s thyroiditis | 0/0 |
| Medication for thyroid disease | 34.3 (7.50–157) |
| Thiamazole | 2/62 (3.2) |
| Levothyroxine | 2/28 (7.1) |

Supplementary Table 3  Odds ratios (95% confidence intervals) of child congenital hypothyroidism (reported on questionnaire) with inland birthplace location

| Mother/child characteristic | Odds ratio (95% confidence interval) |
|-----------------------------|--------------------------------------|
| **Children’s variables**    |                                      |
| Male (vs. female) sex       | 0.49 (0.19–1.32)                     |
| Born at 22–30 weeks (vs. 37–41 weeks of gestation) | 54.2 (14.5–203)         |
| Born at 31–36 weeks (vs. 37–41 weeks of gestation) | 7.10 (2.25–22.4)         |
| Born at ≥42 weeks (vs. 37–41 weeks of gestation) | 0.998 (0.997–0.999)      |
| Twin birth (vs. singleton birth) | 7.38 (1.68–32.5)         |

**Mothers’ variables**

| Iodine supplement intake | 0/1 (0) |
| Seaweed intake ≥3 times per week | 16/5,738 (0.28) |
| Estimated iodine intake <75 μg/day in the 1st trimester | 5/2,348 (0.21) |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 3/2,395 (0.13) |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 1/1,462 (0.07) |
| Estimated iodine intake >2,000 μg/day in the 1st trimester | 0/11 (0) |
| Estimated iodine intake >2,000 μg/day in the 2nd to 3rd trimester | 0/4 (0) |
| Disinfection with povidone iodine at delivery | 3/2,161 (0.14) |
| History of hysterosalpingography | 0/67 (0) |
| Thyroid disease | 3/69 (4.4) |
| Graves’ disease | 1/61 (1.6) |
| Hypothyroidism or Hashimoto’s thyroiditis | 0/0 |
| Medication for thyroid disease | 34.3 (7.50–157) |
| Thiamazole | 2/62 (3.2) |
| Levothyroxine | 2/28 (7.1) |

† Owing to a small number of cases of child congenital hypothyroidism, this odds ratio could not be calculated.
Supplementary Table 4  Incidence rate of child congenital hypothyroidism (reported on questionnaire at 1 year of age) in mothers aged 35 years or more

| Mother/child characteristic | Incidence per 100 children |
|-----------------------------|---------------------------|
| **Children’s variables**    |                           |
| Male sex                    | 16/14,056 (0.11)          |
| Female sex                  | 18/13,067 (0.14)          |
| Born at 22–30 weeks’ gestation | 3/194 (1.55)            |
| Born at 31–36 weeks’ gestation | 1/1,664 (0.06)           |
| Born at 37–41 weeks’ gestation | 30/25,152 (0.12)         |
| Born at ≥42 weeks’ gestation | 0/61 (0)                 |
| Singleton birth             | 34/26,528 (0.13)          |
| Twin birth                  | 0/592 (0)                 |
| **Mothers’ variables**      |                           |
| Iodine supplement intake    | 0/4 (0)                   |
| Seaweed intake ≥3 times per week | 28/22,253 (0.13)           |
| Estimated iodine intake <75 μg/day in the 1st trimester | 12/7,362 (0.16)            |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 8/7,315 (0.11)            |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 3/4,058 (0.07)          |
| Estimated iodine intake >2,000 μg/day in the 1st trimester | 0/46 (0)                 |
| Estimated iodine intake >2,000 μg/day in the 2nd to 3rd trimester | 0/41 (0)                 |
| Estimated iodine intake >2,000 μg/day in the 1st to 3rd trimester | 0/4 (0)                  |
| Disinfection with povidone iodine at delivery | 6/4,110 (0.15)          |
| History of hysterosalpingography | 1/562 (0.18)            |
| Thyroid disease             |                           |
| Graves’ disease             | 5/406 (1.23)              |
| Hypothyroidism or Hashimoto’s thyroiditis | 3/412 (0.73)          |
| Medication for thyroid disease |                         |
| Thiamazole                  | 2/127 (1.57)              |
| Levotyroxine                | 4/343 (1.17)              |

Supplementary Table 5  Odds ratios (95% confidence intervals) of child congenital hypothyroidism (reported on questionnaire) among mothers aged 35 years or more

| Mother/child characteristic | Odds ratio (95% confidence interval) |
|-----------------------------|--------------------------------------|
| **Children’s variables**    |                                       |
| Male (vs. female) sex       | 0.83 (0.42–1.62)                      |
| Born at 22–30 weeks (vs. 37–41 weeks of gestation) | 13.2 (3.98–43.5)                     |
| Born at 31–36 weeks (vs. 37–41 weeks of gestation) | 0.50 (0.07–3.70)                     |
| Born at ≥42 weeks (vs. 37–41 weeks of gestation) | —†                                  |
| Twin birth (vs. singleton birth) | —†                                  |
| **Mothers’ variables**      |                                       |
| Iodine supplement intake    | —†                                   |
| Seaweed intake ≥3 times per week | 1.02 (0.42–2.47)                     |
| Estimated iodine intake <75 μg/day in the 1st trimester | 1.44 (0.71–2.91)                     |
| Estimated iodine intake <75 μg/day in the 2nd to 3rd trimester | 0.81 (0.37–1.80)                     |
| Estimated iodine intake <75 μg/day in the 1st to 3rd trimester | 0.54 (0.17–1.78)                     |
| Estimated iodine intake >2,000 μg/day in the 1st trimester | —†                                   |
| Estimated iodine intake >2,000 μg/day in the 2nd to 3rd trimester | —†                                   |
| Estimated iodine intake >2,000 μg/day in the 1st to 3rd trimester | —†                                   |
| Disinfection with povidone iodine at delivery | 1.21 (0.46–3.24)                     |
| History of hysterosalpingography | 1.37 (0.19–10.1)                      |
| Thyroid disease             |                                       |
| Graves’ disease             | 11.4 (4.41–29.7)                     |
| Hypothyroidism or Hashimoto’s thyroiditis | 6.28 (1.91–20.6)                     |
| Medication for thyroid disease |                                   |
| Thiamazole                  | 13.5 (3.20–56.9)                     |
| Levotyroxine                | 10.5 (3.69–30.0)                     |

† Owing to a small number of cases of child congenital hypothyroidism, this odds ratio could not be calculated.
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