

Clinical Research Article

Thyroid Function of Infants Breastfed by Mothers with Graves Disease Treated with Inorganic Iodine: A Study of 100 Cases

Katsuhiko Hamada,¹ Tetsuya Mizokami,¹ Tetsushi Maruta,¹ Kiichiro Higashi,¹ Kaoru Konishi,² Naoko Momotani,³ and Junichi Tajiri¹

¹Tajiri Thyroid Clinic, Kumamoto, Japan; ²Division of Newborn Screening, Tokyo Health Service Association, Tokyo, Japan; and ³Yotsuya Thyroid Clinic, Tokyo, Japan

ORCID number: 0000-0003-4350-8528 (K. Hamada).

Abbreviations: ATD, antithyroid drug; FT4, free thyroxine; GD, Graves disease; KI, potassium iodide; TRAb, thyrotropin receptor antibody; TSH, thyrotropin.

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Abstract

Context: We previously reported that inorganic iodine therapy in lactating women with Graves disease (GD) did not affect the thyroid function in 25 of 26 infants despite their exposure to excess iodine via breast milk.

Objective: To further assess thyroid function in infants nursed by mothers with GD treated with inorganic iodine.

Design: Case series

Setting: Tajiri Thyroid Clinic, Japan

Participants: One hundred infants of lactating mothers with GD treated with potassium iodide (KI) for thyrotoxicosis

Main Outcome Measures: Infant blood thyrotropin (TSH) and free thyroxine (FT4) levels were measured by the filter paper method. Subclinical hypothyroidism was defined as TSH ≥ 10 μ IU/mL and ≥ 5 μ IU/mL in infants aged < 6 and ≥ 6 months, respectively.

Results: Overall, 210 blood samples were obtained from 100 infants. The median infant age was 5 (range, 0–23) months; median maternal KI dose, 50 (4–100) mg/day; median blood TSH level, 2.7 (0.1–12.3) μ IU/mL; and median blood FT4 level, 1.04 (0.58–1.94) ng/dL. Blood TSH level was normal in 88/100 infants. Twelve infants had subclinical hypothyroidism; among them, blood TSH levels normalized after maternal KI withdrawal or stopping breastfeeding in 3 infants. In 7 infants, blood TSH levels normalized during KI administration without stopping breastfeeding. Two infants could not be followed up.

Conclusion: In Japan, inorganic iodine therapy for lactating women with GD did not affect thyroid function in most of the infants. Approximately 10% of infants had mild subclinical hypothyroidism, but blood TSH level normalized during continued or after discontinuing iodine exposure in all followed up infants.

Key Words: breastfeeding, inorganic iodine, infants, thyroid function, Graves disease

Drug treatment for Graves disease (GD) in lactating women should consider transferability of the drug to the breast milk and the effect of the transferred drug on the infant's thyroid function. Although antithyroid drugs (ATDs) are known to transfer to the breast milk [1-3], ATDs in small to moderate doses for lactating women with GD have been reported to have no adverse effect on the infant's thyroid function [4, 5]. As such, small to moderate amounts of ATDs are also given to breastfeeding mothers with GD [6].

In Japan, inorganic iodine is sometimes used to treat hyperthyroidism in GD patients with mild hyperthyroidism or those who experience ATD-related side effects [7, 8]. Inorganic iodine therapy is also a treatment option for lactating women with GD who cannot tolerate the side effects of ATDs. However, inorganic iodine is concentrated in the mammary gland and excreted in breast milk [9], thus exposing the infants to excess iodine. Because excess iodine can cause hypothyroidism in infants, breastfeeding should generally be avoided during inorganic iodine treatment of lactating mothers. However, many mothers with GD hope for breastfeeding due to its benefits over formula feeding or because infants reject the formula. Therefore, it is important to clarify the effects of inorganic iodine administration to lactating mothers with GD on the thyroid function of their infants.

Large doses of iodine in lactating women have been reported to cause hypothyroidism in their infants [10-13]. However, the mothers in these studies did not have thyroid disease, and the subjects were premature or newborn infants. In our previous study, inorganic iodine therapy in lactating women with GD in Japan, which is an iodine-sufficient country, did not affect the thyroid function in 25 of 26 infants despite their exposure to excess iodine via breast milk [14]. This study aimed to further evaluate the thyroid functions of infants breastfed by mothers with GD treated with inorganic iodine.

Materials and methods

Subjects

We evaluated 100 infants of 81 lactating mothers with GD who were treated with potassium iodide (KI) alone for thyrotoxicosis between February 2008 and February 2017. The 100 infants included the 26 infants evaluated in our previous study [14]. There were 55 infants whose mothers were already receiving KI treatment

before childbirth and 45 infants whose mothers resumed or started KI due to the appearance or exacerbation of thyrotoxicosis after childbirth. KI was administered to patients with mild hyperthyroidism (serum free thyroxine [FT4] level below 4.0 ng/dL and mild symptoms), those with side effects due to ATDs, those who wanted to avoid side effects of ATDs, those who became pregnant while taking methimazole, and those with postpartum thyrotoxicosis in whom it was difficult to differentiate between GD and painless thyroiditis. The KI dose was adjusted every 1 to 3 months to maintain normal maternal thyroid function. Some infants were fully breastfed, whereas others received mixed feeding (ie, breast milk and formula). Informed consent was obtained from all mothers. This case series was approved by our clinical Institutional Review Board.

Assessment of infant thyroid function

The infant's blood levels of thyrotropin (TSH) and FT4 were measured when the mother visited the clinic throughout the period when the mother was taking KI and breastfeeding. In all measurements, blood samples were collected from the outer edge of the footpad using the less invasive and simple filter paper method. Blood TSH and FT4 levels were measured via enzyme-linked immunosorbent assay using dried blotted blood samples. Blood TSH levels were measured using Cretin TSH ELISA II (Eiken Chemical Co., Ltd, Tokyo, Japan) [15] and blood FT4 levels were measured using ENZAPLATE N-FT4 (Siemens Healthcare Diagnostics KK, Tokyo, Japan; normal range 0.65-1.49 ng/dL) [16]. TSH concentrations were expressed as serum concentrations, which were calculated by multiplying the whole blood values by 1.6 [14]. With reference to the expert opinion of congenital hypothyroidism mass screening guidelines (2014 revised edition), subclinical hypothyroidism was defined as a blood TSH level of ≥ 10 μ IU/mL and ≥ 5 μ IU/mL in infants aged < 6 and ≥ 6 months, respectively [17].

Results

Gestational age at birth (weeks) and mass screening test

The 100 infants included 46 boys and 54 girls. The data of gestational age at birth were not available for 12 infants. The median gestational age at birth of the 88 infants was 39 (range, 35-41) weeks. There were 9 preterm infants.

Among them, there were 6 and 3 infants who were born at 35 and 36 weeks of gestational age, respectively. All infants underwent mass screening for congenital hypothyroidism 4 to 7 days after birth, and none of them presented with hypothyroidism according to interviews with mothers. Four infants had transient mild neonatal hyperthyroidism.

Infant thyroid function

In total, 210 blood samples were obtained from the 100 infants. The median age of the infants was 5 (range, 0-23) months, the median maternal KI dose was 50 (4-100) mg/day, the median maternal duration of KI administration from before until after delivery was 298 (13-3082) days, the median infant blood TSH level was 2.7 (0.1-12.3) $\mu\text{IU}/\text{mL}$, and the median infant blood FT4 level was 1.04 (0.58-1.94) ng/dL. **Figure 1** shows the relationship between infant age and blood TSH levels for the 210 samples. Overall, 88 infants (197 samples) had normal TSH levels. In the infant with the highest blood TSH level, the blood TSH level was 12.3 $\mu\text{IU}/\text{mL}$, and the blood FT4 level was 0.87 ng/dL. There were 12 infants (13 samples) who had subclinical hypothyroidism, and the course of blood TSH levels in these

infants is shown in **Fig. 2**. In 3 infants, blood TSH levels normalized within 2 months after maternal KI discontinuation or termination of breastfeeding. In 7 infants, blood TSH levels normalized during KI administration without cessation of breastfeeding (among them, in 3 infants, their mothers reduced breastfeeding frequency because we encouraged them to stop breastfeeding). We could not follow up the course in 2 infants. In one of these infants, the effect of KI monotherapy on thyroid function could not be followed up because the mother used methimazole in addition to KI during treatment.

Thyroid function in infants with lactating mothers with Graves disease who started or resumed taking KI after childbirth

To examine the short-term effects of iodine overload on infants, we examined the relationship between the period of maternal KI administration and infant blood TSH levels in 45 infants (87 samples) of lactating mothers with GD who started or resumed KI after childbirth (**Fig. 3**). Among them, 11 infants (13 samples) had blood TSH levels ≥ 5 $\mu\text{IU}/\text{mL}$, and most of these samples (11 of the 13 samples) had been

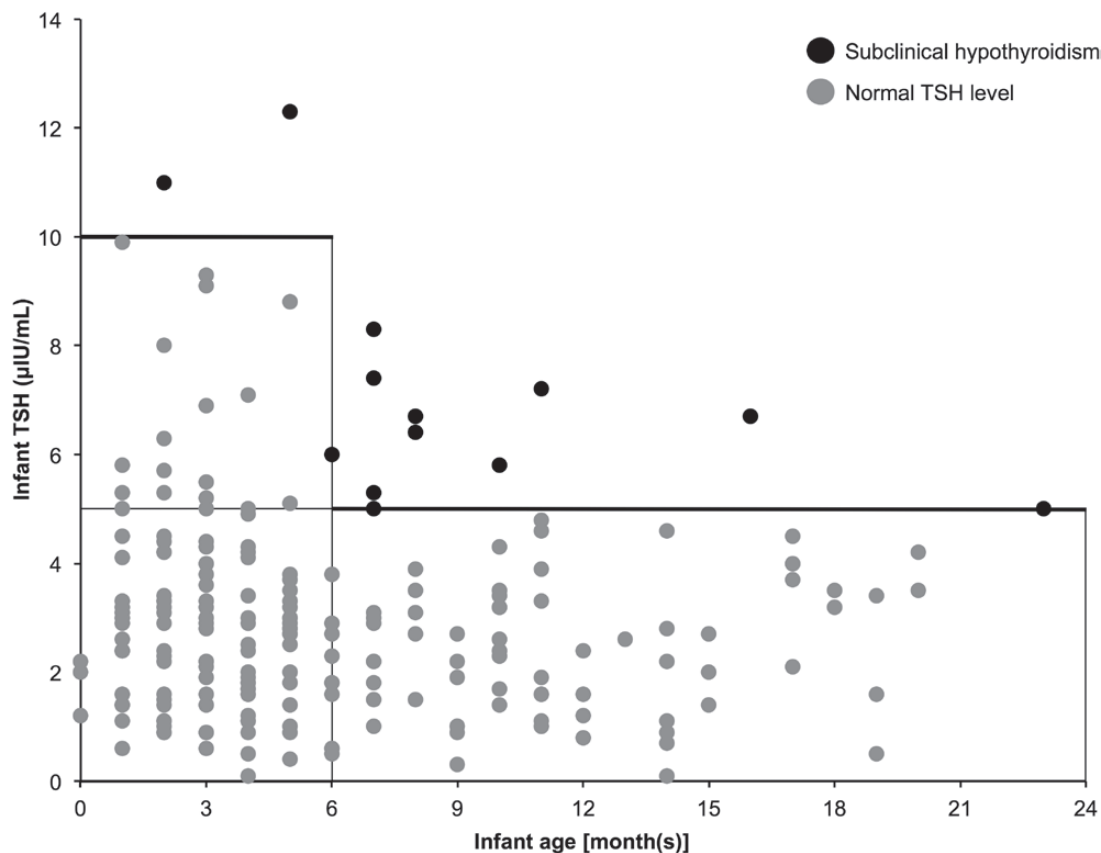


Figure 1. Relationship between infant age and blood TSH levels in infants breastfed by mothers with Graves disease treated with KI. Black and gray circles indicate subclinical hypothyroidism and normal TSH level, respectively. The blood TSH level was normal in 88 infants (197 samples), whereas subclinical hypothyroidism was observed in 12 infants (13 samples).

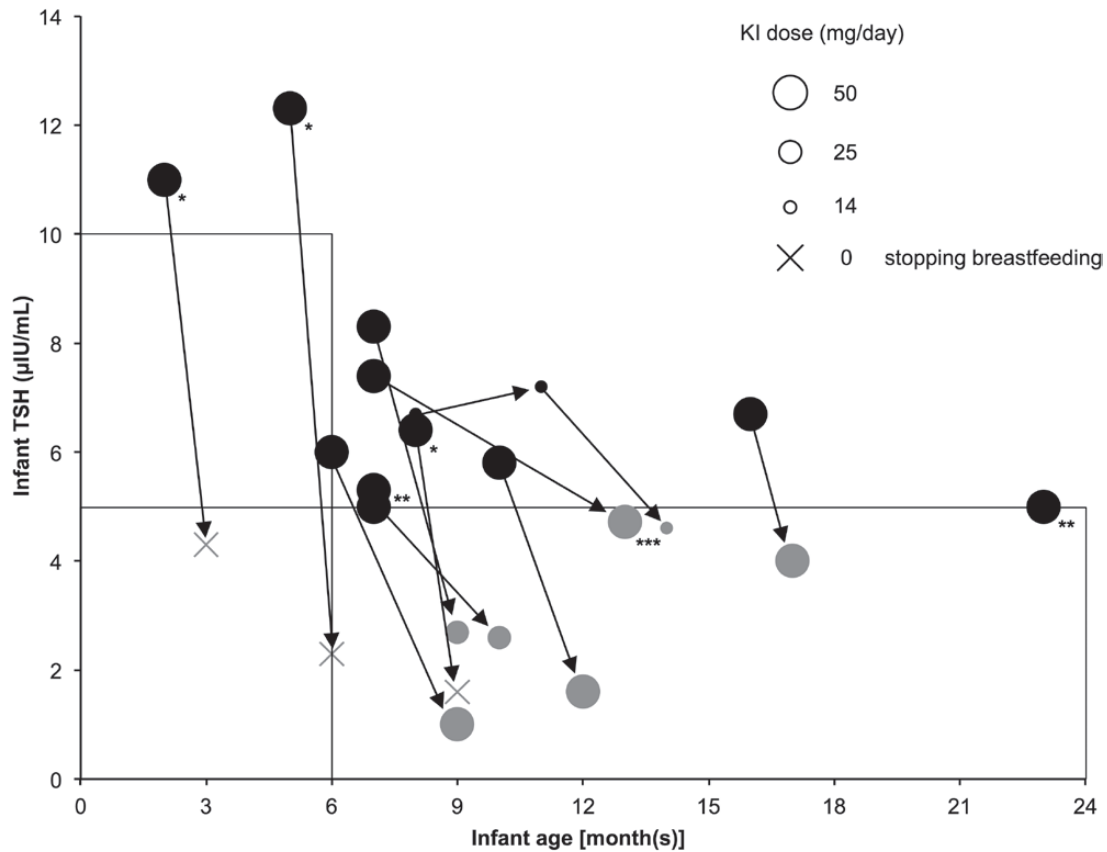


Figure 2. Course of blood TSH levels in the 12 infants with subclinical hypothyroidism. Each circle indicates the KI dose administered to a mother. Arrows indicate data from the same cases. Black and gray circles indicate subclinical hypothyroidism and normal TSH level, respectively. In 3 infants (*), the blood TSH levels normalized due to discontinuation of KI or stopping breastfeeding, whereas the blood TSH levels normalized during KI administration without cessation of breastfeeding in 7 infants. Two infants (***) could not be followed. One blood TSH level test (***) was performed at another hospital; thus the examination method is unknown.

collected immediately after the mother started taking KI. In 3 of these 11 infants, the blood TSH levels decreased to <5 $\mu\text{IU/mL}$ within 2 months after maternal KI withdrawal or stopping breastfeeding. In the remaining 8 infants, the blood TSH level decreased to <5 $\mu\text{IU/mL}$ during KI administration without cessation of breastfeeding (among them, in 3 infants, their mothers reduced breastfeeding frequency because we encouraged them to stop breastfeeding) (Fig. 4).

Discussion

In this study, inorganic iodine administration to lactating mothers with GD did not influence thyroid function, evaluated according to blood TSH levels, in approximately 90% of the 100 evaluated infants. About 10% of the infants had mild subclinical hypothyroidism, but none had overt hypothyroidism.

According to World Health Organization, daily iodine intake during lactation should not exceed 500 $\mu\text{g/day}$ due to the lack of added health benefits and concerns about the potential for impaired thyroid function [18]. The American

Thyroid Association guidelines recommend that iodine intake during breastfeeding should not exceed 500 to 1100 $\mu\text{g/day}$ because of concerns about the risk of infant hypothyroidism [6]. However, the findings of the present study indicate that inorganic iodine administration in lactating women with GD is less likely to cause overt hypothyroidism in infants past the neonatal period. Therefore, we believe that it is not always necessary to prohibit breastfeeding in women with GD being treated with inorganic iodine if they wish to continue breastfeeding. However, given that breastfeeding during inorganic iodine treatment exposes infants to excess iodine [14] and may cause subclinical hypothyroidism in about 10% of infants, it is important to closely monitor the infant's thyroid function during inorganic iodine treatment of lactating mothers with GD. Thyroid hormone is essential for normal brain development in infancy. Thus, it is important to immediately take measures such as discontinuation of inorganic iodine therapy for mothers, cessation of breastfeeding, and administration of levothyroxine to breastfed infants, in the event of subclinical or overt hypothyroidism. Because pre-term infants are reported to be susceptible to excessive iodine

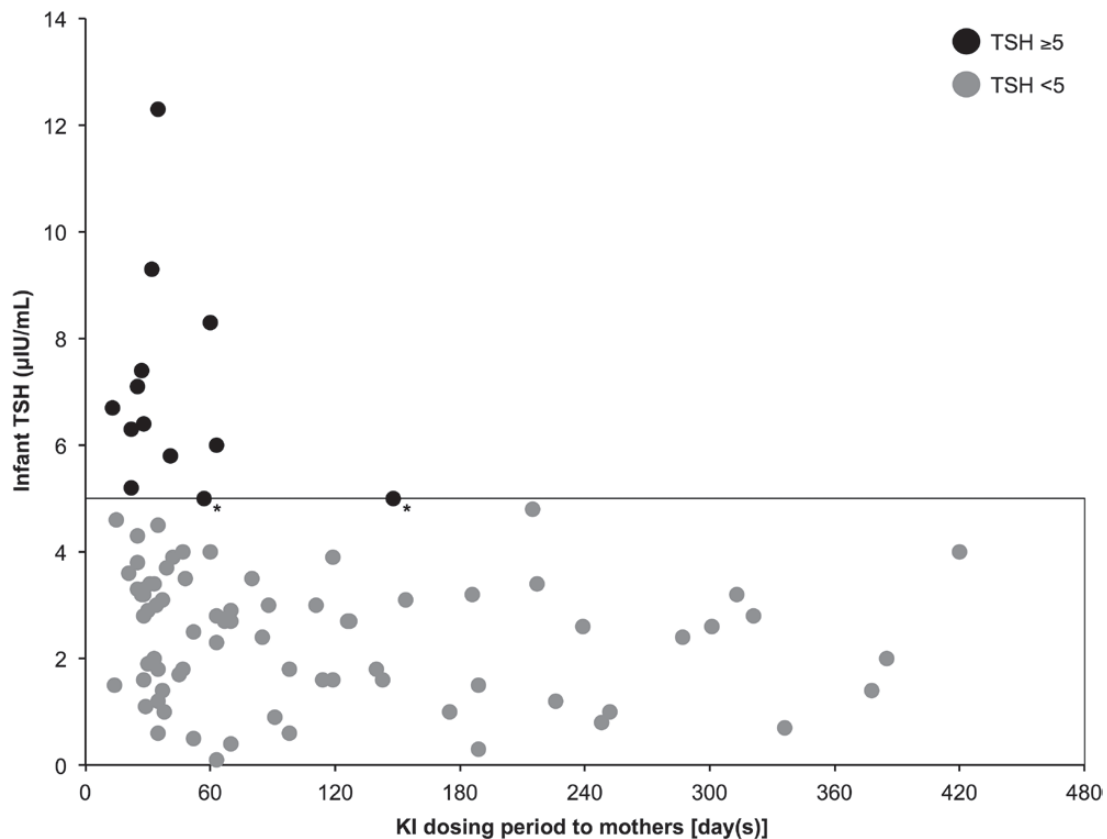


Figure 3. Relationship between the period of maternal KI administration and infant blood TSH levels in infants of lactating mothers with Graves disease who started or resumed KI after childbirth. Black circles indicate blood TSH levels ≥ 5 $\mu\text{IU/mL}$, and gray circles indicate blood TSH levels < 5 $\mu\text{IU/mL}$. Among the 45 infants (87 samples), 11 infants (13 samples) had blood TSH levels ≥ 5 $\mu\text{IU/mL}$. All samples with blood TSH levels ≥ 5 $\mu\text{IU/mL}$, except 2 samples (*), were obtained immediately after the mother started KI.

[13], mothers receiving inorganic iodine treatment should avoid breastfeeding preterm infants. In this study, only 1 of 9 preterm infants had subclinical hypothyroidism, and the preterm infants were not susceptible to excess iodine. One possible cause for this finding is the age of gestation at birth. The premature infants in this study were born at ≥ 35 weeks' gestation, whereas the premature infants in the previous report were born at ≤ 34 weeks' gestation [13].

Inorganic iodine treatment may be an option for mothers with GD with adverse reactions to ATDs who wish to breastfeed but do not wish to undergo surgery for GD. If maternal thyroid function is poorly controlled by inorganic iodine therapy, other therapies (eg, radioactive iodine therapy after stopping breastfeeding, thyroidectomy) should be considered. Inorganic iodine therapy is likely to be effective in patients with mild hyperthyroidism [7], but the factors that predict the efficacy of inorganic iodine therapy before treatment are unknown [8].

In total 88 of the 100 infants in this study had normal TSH levels and 7 of 12 infants with subclinical hypothyroidism became euthyroid despite the continuation of maternal KI without cessation of breastfeeding. Accordingly, we speculated that the infant's thyroid might have escaped

from the Wolff–Chaikoff effect in which excess iodine inhibits thyroid hormone synthesis by blocking organification. The Wolff–Chaikoff effect is generally temporary in normal thyroid glands, with the suppression of thyroid hormone synthesis resolved within a few days through the escape phenomenon [19]. In the analysis of infants whose mothers started KI after childbirth ($n = 45$), most of the samples with blood TSH levels ≥ 5 $\mu\text{IU/mL}$ were collected immediately after starting KI administration to the mothers. In 8 of the 11 infants whose blood TSH levels ≥ 5 $\mu\text{IU/mL}$, the blood TSH levels decreased to < 5 $\mu\text{IU/mL}$ despite maternal KI continuation without stopping breastfeeding. Rat data suggest that the ability of human fetuses to escape from the Wolff–Chaikoff effect develops from 36 to 40 weeks of gestation [20, 21]. The results of this study suggest the possibility of the escape phenomenon from the Wolff–Chaikoff effect in infants.

Our result that infant thyroid function was not easily affected by excess iodine may be related to the fact that Japanese people consume a large amount of iodine daily from seaweeds [22]. As discussed in our previous paper [14], infants in iodine-deficient areas may be more strongly affected by excess iodine. The results of this study may

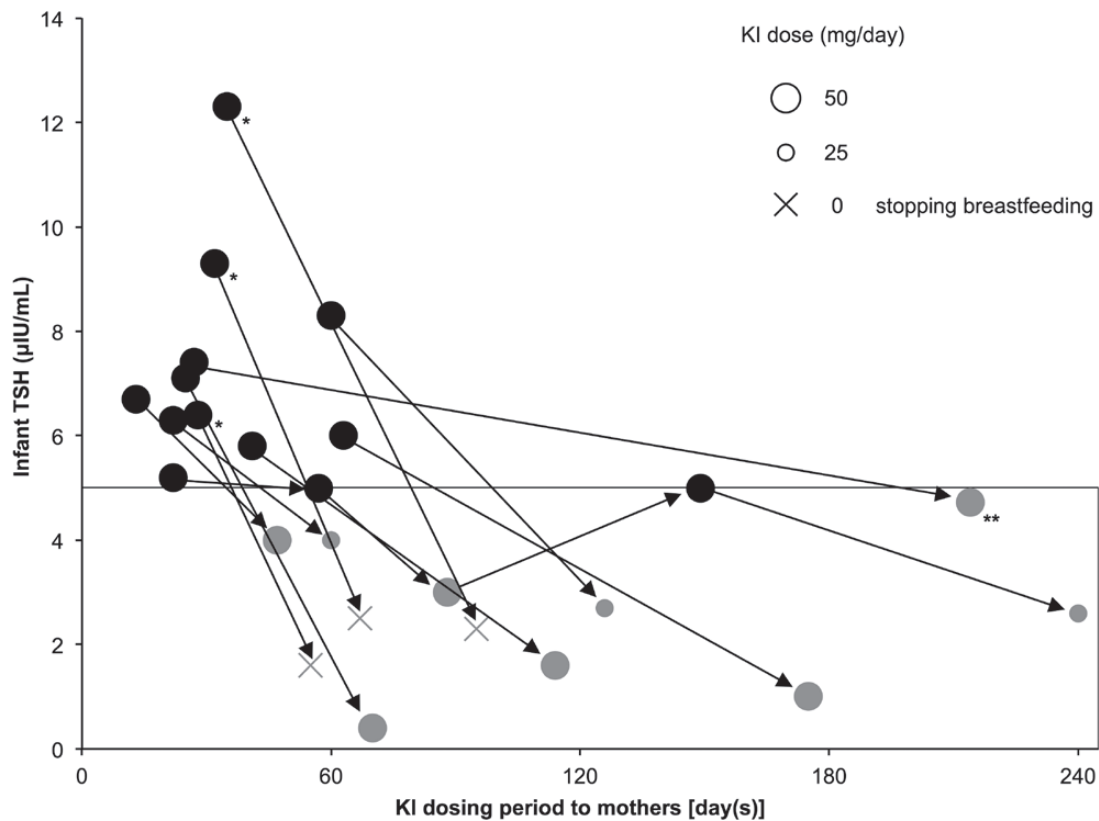


Figure 4. Course of blood TSH levels in 11 infants with blood TSH levels ≥ 5 $\mu\text{IU/mL}$ among infants of mothers with Graves disease who started or resumed KI after childbirth. Each circle indicates the KI dose administered to a mother. Arrows indicate data from the same cases. Black circles indicate blood TSH levels ≥ 5 $\mu\text{IU/mL}$, and gray circles indicate blood TSH levels < 5 $\mu\text{IU/mL}$. In 3 infants (*), the blood TSH levels decreased to < 5 $\mu\text{IU/mL}$ after maternal KI withdrawal or stopping breastfeeding. In 8 infants, the blood TSH levels decreased to < 5 $\mu\text{IU/mL}$ during KI administration without stopping breastfeeding. One blood TSH level test (**) was performed at another hospital; thus the examination method is unknown.

also be associated with maternal TSH receptor antibody (TRAb). If maternal TRAb levels in the third trimester of pregnancy are high, maternal TRAbs that cross the placenta may play a role in protecting against the effects of excess iodine exposure on infant thyroid function for 2 to 3 months after birth.

In our previous study, breast milk and infant urine iodine concentrations were evaluated in 26 infants breastfed by mothers with GD taking KI. We found a high iodine concentration in both breast milk (median 15 050 $\mu\text{g/L}$) and infant urine (median 15 650 $\mu\text{g/L}$). The KI dose was correlated with infant urinary iodine concentration and breast milk iodine concentration. The infant urinary iodine concentration was also correlated with the breast milk iodine concentration. These results clearly showed that maternal KI administration caused excess iodine in infants via breastfeeding [14]. Therefore, we did not measure breast milk and infant urine iodine concentrations for all mothers and infants enrolled in this study to reduce the burden on mothers and infants, except for mothers and infants in whom these concentrations had been measured for the previous study.

Although the current study targeted breastfed infants, detailed information on lactation status (eg, frequency and type [exclusive breastfeeding or mixed feeding] of feeding) was not completely available. Our previous study involving 26 infants found a positive correlation between the iodine concentration in breast milk and that in the infant's urine despite variations in the frequency of breastfeeding for each infant [14]. Therefore, it is speculated that the frequency of breastfeeding does not significantly affect the degree of iodine exposure in infants.

In conclusion, treatment with inorganic iodine for lactating women with GD in Japan, an iodine-sufficient country, did not affect the thyroid function in most of the infants. Approximately 10% of infants developed mild subclinical hypothyroidism; however, their blood TSH levels normalized during continued or after discontinuing iodine exposure in all infants, except in 2 infants who were lost to follow-up. These findings indicate that in an iodine-sufficient area, lactating mothers with GD can be treated with inorganic iodine while carefully considering therapeutic indications and monitoring the infant thyroid function.

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Additional Information

Correspondence: Katsuhiko Hamada, MD, Tajiri Thyroid Clinic, 2-6-3 Suizenji, Chuo-ku, Kumamoto, Kumamoto 862-0950, Japan. Email: hamada@j-tajiri.or.jp.

Disclosures: The authors have nothing to disclose.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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