Dose-Dependent Influence of Antithyroid Drugs on the Difference in Free Thyroxine Levels between Mothers with Graves' Hyperthyroidism and Their Neonates

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Keywords

Antithyroid drugs · Graves' disease · Neonatal thyroid dysfunction · Pregnancy · Thyroxine

Abstract

Background: Several guidelines have recommended that the use of the lowest effective dose of antithyroid drugs (ATDs) that maintains maternal serum free thyroxine (FT4) levels at or moderately above the upper limit of the reference range is appropriate for fetal euthyroid status. However, little is known about whether ATD dosage affects the difference in serum FT4 levels between the mother and neonate. We conducted a retrospective study at a tertiary hospital in Japan to investigate the dose-dependent influence of ATDs on both maternal and fetal thyroid hormone status. **Materials and Methods:** We retrospectively examined 62 pregnant women who delivered between 2007 and 2016

and were treated for Graves' hyperthyroidism with ATD at any stage during pregnancy. We selected individuals whose data on maternal FT4 level within 4 weeks of their deliveries and cord FT4 level of their infants at the time of delivery were available. Those with multiple pregnancies, iodine or glucocorticoid treatment, and fetal goiter detected by ultrasonography were excluded. **Results:** After the exclusion criteria were applied, we recruited 40 individuals. The cord FT4 levels were significantly lower than the maternal FT4 levels in patients treated with high-dosage ATDs (methimazole >5 mg daily or propylthiouracil >100 mg daily). However, there were no significant differences between maternal and cord FT4 levels in patients treated with low-dosage ATDs (methimazole ≤5 mg daily or propylthiouracil ≤100 mg daily). We selected 35 individuals whose data on maternal thyrotropin receptor-binding inhibitory immunoglobulin (TBII) level were available. Multiple linear regression analysis adjusted for ATD dosage, maternal TBII level, and gestational period

found that ATD dosage was a significant predictor of the difference in serum FT4 levels between the mother and neonate. In terms of maternal complications, multiple logistic regression analysis identified maternal free triiodothyronine (FT3) level as a significant predictor of the incidence of preterm delivery. **Conclusions:** We found a dose-dependent influence of ATDs on the difference in serum FT4 levels between mothers with Graves' hyperthyroidism and their neonates. Further studies to evaluate the optimal target FT4 and FT3 levels for the mother and neonate during pregnancy may improve the outcome of pregnant women with Graves' hyperthyroidism.

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Introduction

Antithyroid drugs (ATDs) are the mainstay of medical treatment for Graves' hyperthyroidism, occurring in approximately 0.2% during pregnancy [1]. All ATDs tend to be more potent in the fetus than in the mother [2–4]. ATD dosage that ensures maternal serum free thyroxine (FT4) levels at or moderately above the upper limit of the reference range is reported to be appropriate for fetal euthyroid status [2]. This recommendation was incorporated into the 2017 American Thyroid Association (ATA) management guideline [4], the 2018 European Thyroid Association (ETA) management guideline [5], and the 2019 Japanese Thyroid Association (JTA) management guideline [6].

There is evidence for the dose-dependent influence of ATDs on fetal thyroid hormone status; specifically, Gardner et al. [3] identified a significant inverse correlation between the cord serum FT4 index and the area under the curve for maternal serum propylthiouracil concentrations. ATD dosage was also reported to inversely relate to the cord FT4 index [7]. In contrast, other studies have identified no significant correlation between the ATD dosage and cord FT4 status [2, 8–10]. These inconsistent results may be explained by methodological differences. Uenaka et al. [11] recently reported that ATD dosage was a significant factor related to neonatal thyroid dysfunction in univariable analysis, but not in multivariable analysis. However, little is known on the dose-dependent influence of ATDs on the difference in FT4 levels between maternal and cord blood in patients with Graves' disease (GD) [2, 9]. In this connection, future research proposed by the ATA guidelines task force includes a trial assessing the optimal target FT4 level in pregnant women treated for hyperthyroidism [4].

To investigate the effect of different dosages of ATDs on fetal thyroid hormone status, we conducted a retrospective study at a tertiary hospital in Japan. Several guidelines recommended the target maternal FT4 levels to be around the upper limit of the trimester-specific reference range [4–6], which was mainly supported by a retrospective study by Momotani et al. [2]. The authors obtained blood samples from mothers and umbilical cords and compared their FT4 levels. Therefore, we decided to examine the difference in FT4 levels between the maternal and cord blood (calculated as maternal FT4 – cord FT4) to evaluate the influence of ATD dosage.

Materials and Methods

Study Design

We retrospectively examined 62 pregnant women with GD who delivered at the Seirei Hamamatsu General Hospital between 2007 and 2016 and were treated with ATDs at any stage during pregnancy. The hospital is the largest tertiary hospital in the western part of Shizuoka Prefecture in Japan, where many cases from low-risk to high-risk deliveries are managed [12]. The diagnosis of GD was made before or during pregnancy on the basis of the following criteria: (1) the presence of a goiter, ophthalmopathy, and/or signs of thyrotoxicosis (e.g., tachycardia), (2) elevated free triiodothyronine (FT3) and/or FT4 levels, (3) suppressed thyroid-stimulating hormone (TSH) level, and (4) a positive thyrotropin receptor-binding inhibitory immunoglobulin (TBII) test [6]. ATDs were given in the lowest possible dosage to maintain maternal FT4 levels in a euthyroid or mildly thyrotoxic state based on the trimester-specific reference range [13].

We selected cases in which the data on maternal FT4 level within 4 weeks of their deliveries and cord FT4 level of their infants at the time of delivery were available. Those who had multiple pregnancies, fetal goiter detected by ultrasonography, iodine or glucocorticoid treatment, and change in ATD after the final evaluation of the maternal thyroid hormone status were excluded. The following information were retrieved from the medical record: maternal age at pregnancy; height at pregnancy; weight at delivery; ATD dosage; maternal serum TSH, FT4, and TBII; the presence of cesarean section, preterm delivery (i.e., delivered before 37 gestational weeks), fetal distress, and postpartum hemorrhage; gestational period; cord serum TSH, FT4, and TBII; neonatal sex; body weight; Apgar scores; and the presence of low birth weight, macrosomia, and congenital abnormalities.

Individuals were classified into 3 groups based on the administration dosage at the time of delivery: no-ATD group (discontinued ATD administration), low-dosage group (propylthiouracil ≤ 100 mg daily or methimazole ≤ 5 mg daily), and high-dosage group (propylthiouracil > 100 mg daily or methimazole > 5 mg daily). Little is known about the dose-dependent influence of ATDs on the difference in thyroid hormone status between the mother and neonate in patients with GD. Momotani et al. [14] reported little relationship between the fetal thyroid hormone status and maternal ATD doses when the dosage of propylthiouracil was clas-

Table 1. Characteristics of the groups according to different dosages of antithyroid drugs (ATDs; $n = 40$)

Variables	No-ATD	Low-dosage	High-dosage	<i>p</i> value
Number of cases	17	14	9	
Mothers				
Age ^a	32.8±4.1	32.5±4.9	32.3±5.2	0.963
Body mass index ^a	24.0±2.1	24.5±1.6	26.0±4.4	0.414
Body weight, kg ^a	60.8±6.1	61.7±6.7	64.9±10.7	0.902
Dosage of ATDs, mg ^a	0	50.0±24.0	383.3±261.0***, †††	<0.001
TSH, mIU/L ^b	0.77 [0.14–1.13]	0.01 [0.01–0.55]	0.01 [0.01–0.01]††	0.002
FT4, pmol/L ^a	13.09±1.99*	15.23±3.08	18.66±3.83**, †††	<0.001
FT3, pmol/L ^{b, #}	3.87 [3.47–4.13]	4.82 [3.94–5.84]	5.53 [5.44–6.44]†††	<0.001
TBII, % ^{b, ##}	7.1 [3.7–12.5]	7.8 [4.2–16.5]	30.7 [13.4–70.1]*, ††	0.004
Vaginal/cesarean ^c	13/4	12/2	7/2	0.800
Gestational period, days ^a	274.6±9.0	276.8±10.3	259.4±18.1**, ††	0.004
Preterm/full-term delivery ^c	0/17	1/13	4/5††	0.004
Cord blood				
TSH, mIU/L ^b	3.93 [3.17–5.82]*	8.31 [5.20–11.69]	10.96 [9.75–19.05]†††	0.001
FT4, pmol/L ^a	14.93±1.95	15.32±3.22	13.40±5.00	0.008
TSH below RR, FT4 above RR ^c	1 (5.9%)	1 (7.1%)	1 (11.1%)	0.888
TSH below RR, FT4 within RR ^c	1 (5.9%)	0 (0%)	0 (0%)	0.500
TSH within RR, FT4 above RR ^c	5 (29.4%)	4 (28.6%)	1 (11.1%)	0.550
TSH within RR, FT4 within RR ^c	10 (58.8%)	9 (64.3%)	3 (33.3%)	0.317
TSH within RR, FT4 below RR ^c	0 (0%)	0 (0%)	2 (22.2%)	0.027
TSH above RR, FT4 below RR ^c	0 (0%)	0 (0%)	2 (22.2%)	0.027
TBII, % ^b	5.6 [3.3–7.2]	10.5 [2.9–13.7]	27.1 [14.7–64.1]	0.003
Difference of values between mother and cord blood				
FT4, pmol/L ^a	−1.84±2.77	−0.08±3.87	5.26±6.07**, †††	<0.001
Infants				
Sex, boy/girl ^c	9/8	9/5	4/5	0.802
Body weight, g ^a	2,929±469	3,052±286	2,735±611	0.274
Low birth weight ^c	3 (17.6%)	0 (0%)	2 (22.2%)	0.203
Apgar score at 1 min ^a	8.4±0.5	7.7±2.0	7.8±1.1	0.141
Apgar score at 5 min ^a	9.0±0.0	8.8±0.9	8.8±0.8	0.736
Congenital abnormalities ^c	1 (5.9%)	1 (7.1%)	1 (11.1%)	0.888

Significant *p* values are presented in bold. Continuous variables are expressed as ^a mean ± standard deviation or ^b median with interquartile range in square brackets. The *p* values were derived using ^a one-way analysis of variance, ^b Kruskal–Wallis test, or ^c chi-square test. **p* < 0.05, ***p* < 0.01, ****p* < 0.001 compared with the low-dosage group; ††*p* < 0.01, †††*p* < 0.001 compared with the no-ATD group by ^a Fisher's least significant difference test, ^b Dunnett's multiple comparison test, or ^c Fisher's exact test. The dosage of ATDs was calculated as ATD-to-methimazole ratio of 20:1 or ATD-to-propylthiouracil ratio of 1:1. [#] Maternal free triiodothyronine (FT3) levels in no-ATD, low-dosage, and high-dosage groups were available in 16, 11, and 9 individuals, respectively. ^{##} Maternal thyrotropin receptor-binding inhibitory immunoglobulin (TBII) levels in no-ATD, low-dosage, and high-dosage groups were available in 14, 12, and 9 individuals, respectively. FT4, free thyroxine; RR, reference range; TSH, thyroid-stimulating hormone.

sified into the high (>100 mg daily) and low (≤100 mg) groups. To clarify the difference between our study and the previous one, we classified propylthiouracil >100 mg daily into the high-dosage group. ATD dosage was calculated using ratios of 20:1 and 1:1 for methimazole and propylthiouracil, respectively, according to previous studies [4, 15].

To predict the dose-dependent influence of ATD on the fetal thyroid hormone status using multiple linear regression analyses, we selected individuals whose data on maternal age, maternal body weight, ATD dosage, maternal FT4 level, maternal TBII level, gestational period, and cord FT4 level were available.

Laboratory Methods

Serum TSH and FT4 levels were measured using a chemiluminescent immunoassay method (ARCHITECT TSH, ARCHITECT Free T4, and ARCHITECT Free T3; Abbott Corporation, Tokyo, Japan). Reference ranges used at the Seirei Hamamatsu General Hospital were as follows: TSH 0.35–4.94 mIU/L, FT4 9.01–19.05 pmol/L, and FT3 2.90–4.90 pmol/L. On the basis of the results of a previous study using the ARCHITECT platform [16], the reference ranges for umbilical cord serum in vaginal deliveries were determined as follows: TSH 2.64–27.32 mIU/L and FT4 10.56–16.01 pmol/L. Those in cesarean deliveries were as follows: TSH 2.32–11.85 mIU/L and FT4 10.95–16.41 pmol/L. TSH values less

Fig. 1. a Free thyroxine (FT4) levels of mothers and neonates. The p values were derived using a paired t test. **b** Thyroid-stimulating hormone (TSH) levels of mothers and neonates. The p values were derived using the Wilcoxon rank-sum test. Individuals ($n = 40$) were classified into three groups based on the administration dosage of antithyroid drugs (ATDs) at the time of delivery: no-ATD group (discontinued ATD administration), low-dosage group (propylthiouracil ≤ 100 mg daily or methimazole ≤ 5 mg daily), and high-dosage group (propylthiouracil > 100 mg daily or methimazole > 5 mg daily).

than the minimum detectable level of 0.01 mIU/mL were defined as 0.01 mIU/L.

TBII was measured by radioimmunoassay (TRAb Cosmic I; Cosmic Corporation, Tokyo, Japan); the value $< 10\%$ was defined as the reference range by the manufacturer.

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation or median with interquartile range in parentheses. The Kolmogorov-Smirnov tests demonstrated that the frequency distributions of serum FT4 levels in both the maternal and cord blood were not significantly different from a Gaussian distribution, whereas the TSH, FT3, and TBII levels showed a significant difference. One-way analysis of variance followed by Fisher's least significant difference test, Kruskal-Wallis test followed by Dunnett's test, chi-square test, or Fisher's exact test were used for comparisons among multiple ATD dosage categories. The paired t test was used for comparison between the maternal and cord serum FT4 levels. The Wilcoxon

rank-sum test was used for comparison between the maternal and cord serum TSH levels. The unpaired t test, Mann-Whitney U test, or Fisher's exact test was used for comparisons between full-term and preterm delivery groups.

To examine how factors including ATD dosage affected the difference in FT4 levels between the maternal and cord blood, regression analyses were conducted before and after adjustment. All variables with $p < 0.20$ after simple regression analysis and without collinearity between two variables were investigated using multiple regression analysis. It has been reported that the predictive performance would get worse when strict criteria are applied in the small sample size [17]. We determined $p < 0.20$ to select variables for further multiple regression analysis because of the small number of our cases. For preterm delivery, logistic regression analyses were performed to detect predictors with odds ratio before and after adjustment with variables.

All statistical analyses were conducted using the GraphPad PRISM (version 7.0, GraphPad Software, Incorporated, San Di-

Table 2. Predictors of the difference in free thyroxine (FT4) levels between maternal and cord blood before adjustment ($n = 35$)

Variables	Unadjusted			
	<i>B</i>	95% CI	β	<i>p</i> value
Age (years)	−0.039	−0.442 to 0.364	−0.034	0.845
Body weight (kg)	0.084	−0.151 to 0.318	0.126	0.472
Dosage of ATDs (mg)	0.017	0.010 to 0.023	0.680	<0.001
Maternal FT4 (pmol/L)	1.013	0.677 to 1.350	0.730	<0.001
Maternal FT3 (pmol/L) [#]	1.825	0.618 to 3.031	0.491	0.004
Maternal TBII (%)	0.105	0.032 to 0.178	0.453	0.006
Choice of ATDs (PTU compared to MMI) ^{##}	−3.070	−8.303 to 2.163	−0.271	0.234
Gestational period (days)	−0.095	−0.216 to 0.027	−0.266	0.122
Term pregnancy [*]	2.475	−2.512 to 7.463	0.173	0.320

Significant *p* values are presented in bold. The difference in FT4 levels (pmol/L) between maternal and cord blood was calculated as follows: maternal FT4 – cord FT4. The dosage of antithyroid drugs (ATDs) was calculated as ATD-to-methimazole (MMI) ratio of 20:1 or ATD-to-propylthiouracil (PTU) ratio of 1:1. [#] Maternal free triiodothyronine (FT3) levels were determined in 32 individuals. ^{##} PTU was administered in 14 individuals, and MMI was administered in 7 individuals. ^{*} Preterm delivery compared with full-term delivery. CI, confidence interval; TBII, thyrotropin receptor-binding inhibitory immunoglobulin.

ego, CA, USA) or the BellCurve for Excel (version 3.10, Social Survey Research Information Company, Limited, Tokyo, Japan) software. Statistical significance was defined as $p < 0.05$, with 2-sided *p* values.

Results

We recruited 40 individuals after exclusion criteria were applied. The patients' baseline characteristics are summarized in Table 1. Among the different categories of ATD dosage at the time of delivery, significant differences were observed in laboratory tests for thyroid disorders such as maternal TSH, FT4, FT3, and TBII and the cord TSH, FT4, and TBII. The differences in FT4 levels between the mother and the cord blood (calculated as maternal FT4 – cord FT4) were -1.84 ± 2.77 , -0.08 ± 3.87 , and 5.26 ± 6.07 pmol/L in the no-ATD, low-dosage, and high-dosage groups, respectively. The cord FT4 levels were significantly higher than the maternal FT4 levels in the no-ATD group, whereas the cord FT4 levels were significantly lower than the maternal FT4 levels in the high-dosage group (Fig. 1a). Note that there were no significant differences between maternal and cord FT4 levels in the low-dosage group. In contrast to FT4, the cord TSH levels were significantly higher than the maternal TSH levels in all three groups (Fig. 1b).

To examine how factors including ATD dosage affected the difference in FT4 levels between the maternal and cord blood, we selected 35 individuals whose data on maternal age, maternal body weight, maternal FT4 level, maternal TBII level, gestational period, and cord FT4 level were available. The results of simple linear regression analyses of factors related to the difference in FT4 levels between the maternal and cord blood are presented in Table 2. ATD dosage, maternal FT4 level, and maternal TBII level were found to be significant predictors. ATD dosage affects the maternal thyroid hormone levels; therefore, 3 different adjustments were conducted (Table 3). Model 1 multiple linear regression analysis adjusted for ATD dosage, maternal TBII level, and gestational period revealed that ATD dosage was the only significant predictor ($\beta = 0.865$, $p < 0.001$). Model 2 analysis revealed that ATD dosage and maternal FT4 were significant predictors when maternal FT4 level was added to evaluate the effect of ATD dosage to the difference of FT4 levels between the maternal and cord blood. These results indicated that ATD dosage was a significant predictor of the difference in FT4 levels between the maternal and cord blood irrespective of the absence or presence of maternal FT4 as a confounder. Model 3 analysis found that ATD dosage was the only significant predictor when maternal FT3 level was added to Model 1.

Regarding maternal complications, the gestational period in the high-dosage group was 259.4 ± 18.1 , which was

Table 3. Predictors of the difference in free thyroxine (FT4) levels between maternal and cord blood after adjustment ($n = 35$)

Variables	Model 1				Model 2				Model 3			
	B	95% CI	β	<i>p</i> value	B	95% CI	β	<i>p</i> value	B	95% CI	β	<i>p</i> value
Dosage of ATDs (mg)	0.021	0.011 to 0.032	0.865	<0.001	0.014	0.003 to 0.024	0.549	0.013	0.020	0.009 to 0.032	0.813	0.001
Maternal FT4 (pmol/L)					0.804	0.321 to 1.286	0.579	0.002				
Maternal FT3 (pmol/L) [#]									0.699	-0.824 to 2.222	0.188	0.355
Maternal TBII (%)	-0.054	-0.155 to 0.048	-0.232	0.291	-0.088	-0.179 to 0.002	-0.381	0.055	-0.064	-0.177 to 0.048	-0.277	0.251
Gestational period (days)	0.001	-0.104 to 0.107	0.003	0.982	-0.005	-0.096 to 0.086	-0.014	0.912	0.014	-0.106 to 0.134	0.039	0.812

Significant *p* values are presented in bold. The difference in FT4 levels (pmol/L) between maternal and cord blood was calculated as follows: maternal FT4 – cord FT4. The dosage of antithyroid drugs (ATDs) was calculated as ATD-to-methimazole ratio of 20:1 or ATD-to-propylthiouracil ratio of 1:1. [#] Maternal free triiodothyronine (FT3) levels were available in 32 individuals. Model 1 adjusted analysis: dosage of ATDs, maternal thyrotropin receptor-binding inhibitory immunoglobulin (TBII), and gestational period. Model 2 adjusted analysis: dosage of ATDs, maternal FT4, maternal TBII, and gestational period. Model 3 adjusted analysis: dosage of ATDs, maternal FT3, maternal TBII, and gestational period. CI, confidence interval.

Table 4. Characteristics in the full-term and preterm delivery groups ($n = 40$)

Variables	Full-term delivery	Preterm delivery	<i>p</i> values
Number of cases	35	5	
Mothers			
Age ^a	32.5±4.5	33.6±5.0	0.603
Body mass index ^a	24.4±2.0	26.3±5.8	0.137
Body weight, kg ^a	61.6±6.2	64.9±14.3	0.363
Dosage of ATDs, mg ^a	70.0±143.8	340.0±338.0	0.003
TSH, mIU/L ^b	0.14 [0.01–0.84]	0.01 [0.01–0.01]	0.062
FT4, pmol/L ^a	14.67±3.30	18.07±4.09	0.043
FT3, pmol/L ^{b, #}	4.08 [3.69–5.17]	7.16 [6.14–7.27]	<0.001
TBII, % ^{b, ##}	9.0 [4.3–14.6]	28.3 [19.2–71.1]	0.012
Vaginal/cesarean ^c	27/8	5/0	0.563
Gestational period, days ^a	276.1±7.7	243.2±9.7	<0.001
Cord blood			
TSH, mIU/L ^b	5.82 [3.90–9.37]	10.96 [9.34–67.52]	0.145
FT4, pmol/L ^a	14.63±2.35	15.37±7.54	0.643
TBII, % ^b	6.8 [3.6–12.7]	14.7 [5.0–64.1]	0.341
Difference of values between mother and cord blood			
FT4, pmol/L ^a	0.04±4.02	2.70±9.15	0.255
Infants			
Sex, boy/girl ^c	18/17	4/1	0.356
Body weight, g ^a	2,999±388	2,436±636	0.008
Low birth weight ^c	3 (8.6%)	2 (40.0%)	0.109
Apgar score at 1 min ^a	8.3±0.5	6.2±3.3	<0.001
Apgar score at 5 min ^a	9.0±0.3	8.0±1.4	<0.001
Congenital abnormalities ^c	2 (5.7%)	1 (20.0%)	0.338

Significant *p* values are presented in bold. Continuous variables are expressed as ^a mean ± standard deviation or ^c median with interquartile range in square brackets. The *p* values were derived using ^a unpaired *t* test, ^b Mann-Whitney U test, or ^c Fisher's exact test. The dosage of antithyroid drugs (ATDs) was calculated as ATD-to-methimazole ratio of 20:1 or ATD-to-propylthiouracil ratio of 1:1. [#] Maternal free triiodothyronine (FT3) levels in full-term delivery were available in 31 individuals. ^{##} Maternal thyrotropin receptor-binding inhibitory immunoglobulin (TBII) levels in full-term delivery were available in 30 individuals. FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Table 5. Predictors of preterm delivery before and after adjustment ($n = 35$)

Variables	Unadjusted			Adjusted ¹			Adjusted ²		
	odds ratio	95% CI	<i>p</i> value	odds ratio	95% CI	<i>p</i> value	odds ratio	95% CI	<i>p</i> value
Age (years)	1.087	0.860 to 1.375	0.485						
Body weight (kg)	1.054	0.941 to 1.182	0.361						
Dosage of ATDs (mg)	1.005	1.001 to 1.009	0.038	1.003	0.995 to 1.012	0.471	1.001	0.992 to 1.010	0.828
Maternal FT4 (pmol/L)	1.249	0.967 to 1.613	0.089	0.884	0.524 to 1.492	0.645			
Maternal FT3 (pmol/L) [#]	5.916	1.375 to 25.460	0.017				5.794	1.213 to 27.681	0.028
Maternal TBII (%)	1.047	1.007 to 1.089	0.021	1.038	0.972 to 1.109	0.264	1.007	0.941 to 1.078	0.837

Significant *p* values are presented in bold. The dosage of antithyroid drugs (ATDs) was calculated as ATD-to-methimazole ratio of 20:1 or ATD-to-propylthiouracil ratio of 1:1. [#] Maternal free triiodothyronine (FT3) levels were available in 32 individuals. ¹ Adjusted analysis: dosage of ATDs, maternal free thyroxine (FT4), and maternal TBII. ² Adjusted analysis: dosage of ATDs, maternal FT3, and maternal TBII. CI, confidence interval.

significantly shorter than that in the no-ATD (276.6 ± 9.0) and low-dosage groups (276.8 ± 10.3 ; Table 1). In line with this, the incidence of preterm delivery in the high-dosage group was most frequent among the three groups. When comparing the characteristics in the full-term delivery with those in the preterm delivery, significant differences were observed in ATD dosage and maternal FT4, FT3, and TBII (Table 4). Subsequent simple logistic regression analyses revealed that ATD dosage and maternal FT3 and TBII levels were significant predictors of preterm delivery. Multiple logistic regression analysis adjusted for ATD dosage, maternal FT4, and maternal TBII identified no significant predictors, whereas multivariable analysis adjusted for ATD dosage, maternal FT3, and maternal TBII revealed that maternal FT3 level was the only significant predictor (odds ratio, 5.794; $p = 0.028$; Table 5). With regard to neonatal sex, body weight, Apgar scores, and the presence of low birth weight and congenital abnormalities, there were no significant differences among the three groups. Fetal distress, postpartum hemorrhage, and macrosomia were not identified in this study.

Discussion

We retrospectively examined pregnant women with GD at a tertiary hospital in Japan and found a dose-dependent influence of ATDs on the difference in serum FT4 levels between the mother and neonate (Tables 1, 3). The strength of our study lies in the premise that confounding factors of fetal thyroid function were taken into consideration other than the ATD dosage.

Thyroid hormones are critical for the normal development of the central nervous system. In several recent

studies, even mild maternal thyroid hormone insufficiency during the perinatal period was revealed to be associated with a potential risk of brain development impairment [18]. Evaluation of the fetal thyroid status can be achieved through a combination of imaging modalities, such as ultrasonography and magnetic resonance imaging, cordocentesis, and amniocentesis [19]. However, each method has an important shortcoming. Imaging modalities have a limited ability to detect slight fetal thyroid dysfunctions without goiter formation. Cordocentesis, the gold standard diagnostic method to evaluate the fetal thyroid hormone status, is invasive and technically demanding. Amniotic fluid sampling is safer than cordocentesis, but the thyroid hormone status in the amniotic fluid may not accurately reflect the fetal thyroid hormone status. In contrast to these methods, measuring the maternal thyroid hormone status is currently a convenient and reliable approach to monitor the fetal thyroid hormone status [4–6, 10].

The fetus is dependent on the transplacental passage of maternal supply of thyroid hormones before the onset of fetal thyroid function during mid-gestation [10]. Once the fetal thyroid gland becomes functional, TSH-receptor autoantibodies, such as thyroid-stimulating antibodies and thyroid-blocking antibodies that are able to cross the placenta, affect the fetal thyroid gland in pregnant women with GD. Mortimer and coworkers [7] reported that the maternal TBII at delivery was well correlated with maternal cord TBII (Pearson's *r* value, 0.940; $p < 0.001$). ATDs given to the mother also cross the placenta, but the fetal thyroid responds more strongly to ATD therapy than the maternal thyroid. This could be the reason why ATD dosages sufficient to maintain mothers in a euthyroid state often induce fetal hypothyroidism [4].

The ETA, ATA, and JTA guidelines have recommended the lowest effective dose of ATDs to maintain maternal serum FT4 levels at (or just above) the upper limit of the trimester-specific reference range [4–6], which was supported by the previous study by Momotani et al. [2]. By selecting 43 pregnant women with GD who were treated with ATDs at the time of delivery, the authors found that serum FT4 levels were lower in the cord bloods than in the maternal bloods. However, ATD dosage was not taken into consideration in the ETA, ATA, and JTA guidelines. Thus, we evaluated whether ATD dosage affects the difference in FT4 levels between the mother and neonate. To the best of our knowledge, this is the first study of its kind.

Importantly, there were no significant differences between the maternal and cord FT4 levels in the low-dosage group (Fig. 1). It is possible that the fetus may be undertreated, when the maternal FT4 levels are set around the upper limit of the reference range treated with low-dosage ATDs. The undertreatment of maternal hyperthyroidism has been reported to result in central congenital hypothyroidism [20]. Accordingly, we propose to replace the present statement in the guidelines with the following sentences: “Targeting maternal FT4 levels should not exceed the upper limit of the trimester-specific reference range when administering low dosage of ATDs (propylthiouracil ≤ 100 mg daily or methimazole ≤ 5 mg daily). Targeting maternal FT4 levels should be at or just above the upper limit of reference range according to ATD dosage when administering high dosage of ATDs (propylthiouracil > 100 mg daily or methimazole > 5 mg daily).”

The small sample size is a weakness of our study. Guidelines have recommended being stably euthyroid before attempting pregnancy; hence, it seems to be difficult to recruit pregnant patients with GD treated with high-dosage ATDs. A large-scale, multi-institutional joint research that evaluates optimal target FT4 levels based on the different ATD dosages would be required to provide enough high-quality evidence to modify the statements in the present guidelines.

Of additional interest is the finding that the standard deviation of the differences in FT4 levels between the mother and cord blood was 2.77, 3.87, and 6.07 pmol/L in the no-ATD, low-dosage, and high-dosage groups, respectively (Table 1). Although mean maternal FT4 levels were highest in the high-dosage group, note that cord thyroid hormone status in this group was overt hypothyroidism in 2 of 9 neonates. In the current guidelines, ATD administration at the lowest effective dose is recommended to minimize adverse effects. This recommendation

may also be supported by our findings in which the discrepancy between the mother and cord FT4 levels seemed to be ATD dose dependent. We also propose that ATD dosage should be reduced as much as possible using adequate treatment before women with GD attempt pregnancy.

Thionamides that are most frequently used during pregnancy are propylthiouracil and methimazole [2]. In 1977, an *in vivo* study found that the human placenta was more permeable to methimazole than to propylthiouracil [21]; however, a subsequent *in vitro* study revealed that both drugs had similar placental transfer kinetics [22]. Furthermore, other studies have indicated that these two drugs are comparable in GD treatment at least in terms of fetal hypothyroidism-inducing potential [7, 14]. In this connection, our study added the additional evidence that propylthiouracil and methimazole are comparable even in terms of the influence on the difference in FT4 levels between maternal and cord blood (Table 2).

Thyroid function should be controlled not only in the fetus but also in the mother [23]. Moreover, poor control of thyrotoxicosis is associated with several maternal disorders including preeclampsia, congestive heart failure, and preterm delivery [4]. For example, Millar et al. [24] reported that the risk of preterm delivery was significantly higher (odds ratio, 16.5) among women who had hyperthyroidism at presentation and delivery compared with women who had euthyroidism during pregnancy. In agreement with the previous study, our multiple logistic regression analysis identified the maternal FT3 level as a significant predictor of the incidence of preterm delivery. These findings suggest that undertreatment should be avoided in terms of maternal complications. Further studies are needed to assess the optimal maternal FT3 level in addition to FT4 level that is appropriate for both mothers and neonates.

This study has the following limitations. First, its retrospective design has the potential for introducing biases. Second, the maximum duration from maternal blood sampling to cord blood sampling was 4 weeks, which cannot exclude the possible changes of maternal thyroid hormone in this period. In addition, pregnancy is associated with significant and reversible changes influencing the thyroid hormone status. For example, maternal serum thyroxine-binding globulin concentrations increase during the first half of gestation [25]. Thus, our findings may not apply to other periods during pregnancy. Third, reference intervals of thyroid function tests from the umbilical cord blood were not established in our hospital, although the reference ranges for umbilical cord serum

have been reported to be affected by several factors including lifestyle and other environmental factors for every population in different regions even within a country [26]. Last, the possible discrepancy of ATD dosage between the medical record and actual consumption cannot be excluded because patient medication compliance was not monitored.

In conclusion, we analyzed 40 pregnant women with Graves' hyperthyroidism and obtained several important findings. First, the dose-dependent effect of ATDs on the difference in FT4 levels between the mother and neonate was confirmed in patients with GD. Particularly, no significant differences between maternal and cord FT4 levels were observed in the low-dosage group. On the basis of these findings, ATD dosage that ensures FT4 levels at or just above the upper limit of the trimester-specific reference range may not be appropriate when administering low-dosage ATDs. Second, the variation in the discrepancy between maternal and cord FT4 levels was smaller in the low-dosage group than in the high-dosage group, suggesting that minimizing the use of ATDs before attempting pregnancy would be recommended in terms of controlling FT4 levels. Third, maternal FT3 level was identified as an independent predictor of the incidence of preterm delivery. Further studies to assess the optimal maternal target FT4 and FT3 levels for both the mother and neonate during pregnancy may improve the outcome in pregnant women with Graves' hyperthyroidism.

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Statement of Ethics

The study protocol was approved by the Institutional Review Boards of Seirei Hamamatsu General Hospital (No. 2264) and was congruent with the Declaration of Helsinki. Written informed consent was waived because of the retrospective design.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.I. designed the study, collected and analyzed data, and wrote the paper. K.O. analyzed data, wrote the paper, and organized the study. E.O. analyzed data and wrote the paper. T.M., Y.K., C.H., A.M., and S.S. collected and analyzed data. T.S. and Y.O. analyzed data and revised the manuscript. R.G. designed the study, collected and analyzed data, and revised the manuscript.

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