

# Maternal Urinary Triclosan Concentration in Relation to Maternal and Neonatal Thyroid Hormone Levels: A Prospective Study

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**BACKGROUND:** Triclosan (TCS) is a synthetic antibacterial chemical widely used in personal care products. TCS exposure has been associated with decreased thyroid hormone levels in animals, but human studies are scarce and controversial.

**OBJECTIVE:** We evaluated the association between maternal TCS exposure and thyroid hormone levels of mothers and newborns.

**METHODS:** TCS was measured by high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) in urine samples collected during gestational weeks  $38.8 \pm 1.1$  from 398 pregnant women in a prospective birth cohort enrolled in 2012–2013 in Shanghai, China. Maternal serum levels of free thyroxine (FT<sub>4</sub>), thyroid-stimulating hormone (TSH), and thyroid peroxidase antibody (TPOAb) were obtained from medical records. Cord blood levels of free triiodothyronine (FT<sub>3</sub>), FT<sub>4</sub>, TSH, and TPOAb were measured. Multiple linear and logistic regression models were used to examine the relationship between maternal urinary TCS and thyroid hormone levels.

**RESULTS:** TCS was detectable ( $\geq 0.1$  ng/mL) in 98.24% of maternal urine samples with tertile of urinary TCS levels: low ( $< 0.1$ – $2.75$   $\mu\text{g/g.Cr}$ ), medium ( $2.75$ – $9.78$   $\mu\text{g/g.Cr}$ ), and high ( $9.78$ – $427.38$   $\mu\text{g/g.Cr}$ ). With adjustment for potential confounders, cord blood log(FT<sub>3</sub>)pmol/L concentration was 0.11 lower in newborns of mothers with medium and high urinary TCS levels compared with those with low levels. At third trimester, the high TCS concentration was associated with 0.03 [95% confidence interval (CI)  $-0.08$ ,  $-0.02$ ] lower maternal serum log(FT<sub>4</sub>)pmol/L, whereas the medium TCS concentration was associated with 0.15 (95% CI:  $-0.28$ ,  $-0.03$ ) lower serum log(TSH)mIU/L with adjustment for covariates.

**CONCLUSIONS:** Our results suggest significant inverse associations between maternal urinary TCS and cord blood FT<sub>3</sub> as well as maternal blood FT<sub>4</sub> concentrations at third trimester. <https://doi.org/10.1289/EHP500>

## Introduction

Triclosan (TCS) is a synthetic liposoluble broad-spectrum bacteriostatic germicide to varieties of bacteria, fungi, and viruses (Ahn et al. 2008). It has been widely used in personal care products such as toothpastes, soaps, shampoos, and cosmetics with concentrations of 0.1–0.3% for more than 40 years (Jones et al. 2000). After being absorbed into the human body, TCS is mainly excreted via urine (Krishnan et al. 2010). In pregnant women, maternal serum TCS can pass through the placental barrier and reach the fetus, evidenced by its detection in the umbilical cord blood of newborns (Peters 2005).

The structure of TCS resembles thyroxine (T<sub>4</sub>), and previous researchers have found TCS might disrupt thyroid hormone levels (Allmyr et al. 2009; Dann and Hontela 2011). Animal studies have shown that TCS exposure significantly decreases serum totals of the hormones T<sub>4</sub> (Crofton et al. 2007; Paul et al. 2010) and triiodothyronine (T<sub>3</sub>) (Paul et al. 2010) in a dose-dependent manner in rats and reduced total T<sub>4</sub> in pregnant rats (Axelstad et al. 2013). A few epidemiologic studies have examined this topic in humans (Cullinan et al. 2012; Geens et al. 2015) and have generated conflicting results. Specifically, a recent study reported an inverse association between TCS and FT<sub>4</sub> levels in women (Geens et al. 2015). An U.S. national study observed a

positive association between TCS and total T<sub>3</sub> concentrations in adolescents (Koeppel et al. 2013).

Proper thyroid hormone levels are critical for fetal growth and maintaining pregnancy (Sarkhail et al. 2016). During early pregnancy, the fetus relies entirely on transplacental transfer of maternal thyroid hormones and normal maternal thyroid function (Patel et al. 2011). Maternal thyroid homeostasis also contributes substantially to fetal development during the remaining part of pregnancy (Patel et al. 2011). Even minor changes in thyroid homeostasis may affect fetal neurological development. For example, significant lower intelligence quotient (IQ) scores were observed in children of women with thyroid deficiency during pregnancy, even though hormone levels were inside the population reference range (Haddow et al. 1999; Morreale de Escobar et al. 2000).

Exposure to thyroid-disrupting chemicals may result in altered serum thyroid hormone levels, which may have adverse effects on developing fetuses. However, the effect of TCS exposure on maternal and neonatal thyroid hormone levels is unclear. To our knowledge, no previous study has examined this topic in pregnant women. Therefore, we aimed to evaluate the association between maternal TCS exposure and thyroid hormone levels of mothers and newborns.

## Methods

### Study Design and Participants

This study used data from the Shanghai Obesity and Allergy Cohort, a prospective birth cohort study initiated and maintained at the International Peace Maternity and Child Hospital (IPMCH) in Shanghai, China. The primary objective of this cohort study is to examine environmental and maternal risk factors of childhood obesity and allergic diseases. Eligible study participants were recruited at the IPMCH ( $n=680$ ) between June 2012 and February 2013. Eligibility criteria included singleton pregnancy, gestational age  $\geq 28$  weeks, and Shanghai residency with intention to remain in Shanghai for the following 2 years. A face-to-face questionnaire interview was conducted at enrollment to

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collect demographic information including age, education level, maternal weight before pregnancy, and smoking and alcohol consumption before and during pregnancy. Medical history, including thyroid disease before and during pregnancy was abstracted from medical records. A spot urine sample was also collected for measuring TCS concentration during gestational weeks  $38.8 \pm 1.1$  and was stored at  $-80^\circ\text{C}$  until analysis. At the time of delivery, cord blood was collected from newborns and centrifuged to obtain the serum fractions.

Of 680 eligible women who were enrolled, those with assisted conception ( $n = 15$ ) or syphilitic disease ( $n = 3$ ) were excluded. Thirty-nine subjects did not have urine samples collected and were excluded. Also, women with urine samples with creatinine concentrations of  $\leq 0.05 \text{ g/L}$  or  $\geq 3.0 \text{ g/L}$  were excluded ( $n = 3$ ). Among the remaining 620 women, 430 cord blood samples were collected from their newborns with 1 sample per newborn. In addition, women with diagnosed hypothyroidism, subclinical hypothyroidism, and hyperthyroidism before pregnancy were excluded ( $n = 11$ ). Women with gestational hyperthyroidism, hypothyroidism, or subclinical hypothyroidism were also excluded ( $n = 21$ ) (Perinatal Medicine Branch of Chinese Medical Association 2012). In the final analysis, 398 mother–infant pairs were included.

We obtained signed informed consent from all participants and the study was approved by the institutional review board of the Xinhua hospital, Shanghai Jiao Tong University School of Medicine and IPMCH.

### Measurement of Maternal Urinary TCS Concentration

Urinary TCS concentration was quantified using high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS, Agilent 1290–6490, Agilent Technologies Inc, USA) (Chen et al. 2012). First, we used ammonium acetate buffer ( $\text{pH} = 5.0$ ,  $1 \text{ mmol/L}$ ) to dilute  $4 \text{ mL}$  of urine sample and internal isotope to  $6 \text{ mL}$ , then used  $\beta$ -glucuronides (Type H-1 from Helix Pomatia, Sigma-Aldrich) to deconjugate and incubated the samples at  $37^\circ\text{C}$  overnight. Second, we used solid-phase extraction ( $500 \text{ mg/3 mL}$ ; Supelco, ENVI-18) to purify the samples and centrifuged them using a high-speed vacuum centrifuge (Thermos. co, Thermo SPD 121P); then the residue was dissolved in  $20 \mu\text{L}$  methyl alcohol. Finally, we injected these pretreated samples into the HPLC-MS/MS system. The limit of detection (LOD) was  $0.1 \text{ ng/mL}$  (based on a signal-to-noise ratio of 3). Quality assurance and quality control (QA/QC) procedures were carried out for all analyses (Westgard et al. 1981) to avoid external contamination. To account for differences in urinary analyte concentrations caused by urine dilution, the urinary TCS concentration was normalized to creatinine concentration (Koepe et al. 2013), which was measured using Enzymatic Creatinine\_2 Reagents (ECRE\_2) on a discrete analyzer (7100 Hitachi, Tokyo, Japan).

### Measurement of Thyroid Hormones in Cord Blood

Cord blood serum samples were collected and kept at  $-80^\circ\text{C}$  until thyroid hormones were assayed. Serum of cord blood free triiodothyronine ( $\text{FT}_3$ ),  $\text{FT}_4$ , thyroid-stimulating hormone (TSH), and thyroid peroxidase antibody (TPOAb) concentrations were determined by chemiluminescent microparticle immunoassay using the Architect system (Abbott Laboratories, Abbott Park, IL, USA). QA/QC procedures were performed for all thyroid hormones analyses in accordance with Architect system.

### Maternal Thyroid Function

We abstracted maternal thyroid function during pregnancy from medical records. Maternal serum  $\text{FT}_4$ , TSH, and TPOAb levels were screened during the first ( $\leq 13$  weeks gestation), second ( $14\text{--}27$  weeks), and third ( $\geq 28$  weeks gestation) trimesters when participants underwent their routine prenatal care at the IPMCH. During our study period, maternal serum  $\text{FT}_4$  and TSH in the first and the second trimester were measured by electrochemiluminescent microparticle immunoassays using the Architect system (Roche GmbH, Mannheim, Germany).  $\text{FT}_4$  and TSH in the third trimester as well as TPOAb were measured via chemiluminescent microparticle immunoassay using the Architect system (Abbott Laboratories, Abbott Park, IL, USA).

Diagnosis of gestational hyper/hypothyroidism was made by the treating obstetrician based on guidelines for diagnosing and treating thyroid diseases during and after pregnancy for the Chinese population (Endocrinology Branch of Chinese Medical Association 2012). The reference intervals were  $12.91\text{--}22.35 \text{ pmol/L}$  for  $\text{FT}_4$  and  $0.05\text{--}5.17 \text{ mIU/L}$  for TSH at the first trimester by Roche's Architect system;  $9.81\text{--}17.26 \text{ pmol/L}$  for  $\text{FT}_4$  and  $0.39\text{--}5.22 \text{ mIU/L}$  for TSH at the second trimester by Roche's Architect system. At the third trimester, the reference intervals of  $\text{FT}_4$  and TSH were  $9.63\text{--}18.33 \text{ pmol/L}$  and  $0.28\text{--}5.07 \text{ mIU/L}$  respectively by Abbott's Architect system (Endocrinology Branch of Chinese Medical Association 2012). The normal clinical range of serum TPOAb by Abbott's Architect system is below  $5.61 \text{ IU/mL}$  (Wang et al. 2013). All subjects accepted treatment after they were diagnosed with gestational hyperthyroidism or hypothyroidism or subclinical gestational hypothyroidism in our cohort. Therefore, we excluded these women in the final analysis to reduce bias.

Because the urinary samples for determining maternal TCS exposure levels were collected during gestational weeks  $38.8 \pm 1.1$ , we examined the TCS-associated changes of thyroid hormone levels at third trimester.

### Statistical Analysis

Concentrations of urinary TCS and serum thyroid hormones below the LOD were replaced with values equal to the LOD divided by the square root of 2 (Li et al. 2013). Because TCS and thyroid hormone concentrations were not normally distributed, the data were  $\log_{10}$ -transformed for TCS, and natural log-transformed for thyroid hormone concentrations. We used urinary creatinine concentrations to correct urinary TCS concentrations:

$$\begin{aligned} \text{Creatinine-corrected TCS} &= \text{TCS (ng/mL)} / (\text{Cr (g/L)}) \\ &= \text{TCS} / \text{Cr} (\mu\text{g/g.Cr}) \end{aligned}$$

To compare maternal urinary triclosan (TCS) concentration by characteristics of mothers and their infants, Student's *t*-test and ANOVA *F*-test were used.

We also grouped the study participants into low, medium, and high tertiles based on their maternal urinary TCS levels. To examine associations between maternal urinary TCS levels and maternal and cord blood thyroid hormone levels, multiple linear regression models were performed for the continuous variable of thyroid hormone concentrations as a dependent variable, and multiple logistic regressions were used for binary outcome variables (positive vs. negative TPOAb). Model 1 was unadjusted; Model 2 was adjusted for potential confounders, which included maternal age, education level, passive smoking, parity, gestational age at delivery (for cord blood thyroid hormone measures as outcomes), or gestational age when maternal thyroid hormones

**Table 1.** The characteristics of 398 mothers and their infants, and maternal urinary triclosan (TCS) concentration.

Characteristic	Log <sub>10</sub> TCS/Cr (μg/g Cr)		p-Value
	n	mean ± SD	
Maternal age (years)			
<30	202	0.81 ± 0.71	0.13
30–35	172	0.71 ± 0.60	
>35	24	0.97 ± 0.67	
Maternal education			
High School or lower	22	0.90 ± 0.55	0.53
College	331	0.77 ± 0.66	
Master's degree or above	44	0.78 ± 0.74	
Prepregnancy BMI (kg/m <sup>2</sup> )			
<18.5	61	0.86 ± 0.65	0.49
18.5–24.9	294	0.76 ± 0.66	
≥25	43	0.82 ± 0.70	
Husband smoked during pregnancy			
No	295	0.77 ± 0.67	0.70
Yes	98	0.80 ± 0.64	
Gestational age (weeks)			
<37	6	0.77 ± 0.12	0.93
37–40	367	0.77 ± 0.67	
>40	25	0.83 ± 0.57	
Parity			
0	347	0.77 ± 0.67	0.81
≥1	51	0.80 ± 0.64	
Infant sex			
Male	215	0.79 ± 0.60	0.75
Female	183	0.77 ± 0.62	
Neonatal TPOAb			
Negative <sup>a</sup>	364	0.78 ± 0.66	0.84
Positive <sup>b</sup>	34	0.76 ± 0.71	
Maternal TPOAb			
Negative <sup>a</sup>	357	0.78 ± 0.67	0.74
Positive <sup>b</sup>	41	0.74 ± 0.62	

Note: TPOAb, thyroid peroxidase antibody.

<sup>a</sup>TPOAb negative: <5.61 IU/mL.

<sup>b</sup>TPOAb positive: ≥5.61 IU/mL.

were measured; Model 3 was additionally adjusted for prepregnancy body mass index (BMI) categories based on the World Health Organization classification (WHO 2000). Women were divided into three weight levels: normal weight defined as BMI of 18.5–24.99 kg/m<sup>2</sup>, underweight as BMI of <18.5 kg/m<sup>2</sup>, overweight and obese as BMI of ≥25 kg/m<sup>2</sup>. We computed the percent changes of thyroid hormone concentrations for each 10-fold increase in maternal urinary TCS concentration by the following formula:  $e^{\beta} - 1 \times 100$ , where  $\beta$  = coefficient from the multiple regression models.

**Table 2.** The distribution of maternal urinary triclosan (TCS), cord blood thyroid hormone, and maternal serum thyroid hormone concentration at the third trimester.

Concentration	n	GM (95% CI)	25th	50th	75th	95th	Range
Maternal urine TCS measures							
TCS (ng/mL)	398	2.87 (2.47, 3.30)	1.06	2.52	7.69	37.85	LOD <sup>a</sup> –89.36
Creatinine (g/L)	398	0.48 (0.45, 0.51)	0.29	0.54	0.81	1.42	0.05–2.01
Creatinine-adjusted TCS (μg/g Cr)	398	6.00 (5.16, 6.96)	2.12	4.83	16.90	87.74	0.04–427.38
Cord blood thyroid hormones							
FT <sub>3</sub> (pmol/L)	391	1.61 (1.55, 1.65)	1.54	1.72	2.02	2.46	LOD <sup>b</sup> –3.73
FT <sub>4</sub> (pmol/L)	396	13.70 (13.57, 13.90)	12.90	13.78	14.68	16.25	LOD <sup>c</sup> –18.44
TSH (mIU/L)	396	5.49 (5.21, 5.75)	3.96	5.01	6.90	15.57	1.73–39.16
Maternal serum thyroid hormones <sup>d</sup>							
FT <sub>4</sub> (pmol/L)	378	12.43 (12.30, 12.55)	11.60	12.40	13.50	14.80	8.7–16.2
TSH (mIU/L)	378	1.50 (1.43, 1.58)	1.17	1.54	2.10	3.17	0.18–4.82

Note: FT<sub>3</sub>, free triiodothyronine; FT<sub>4</sub>, free thyroxine; GM, geometric mean; TSH, thyroid-stimulating hormone.

<sup>a</sup>TCS limit of detection (LOD) = 0.1 ng/mL. TCS concentrations were ≥LOD in 98.24% of maternal urine samples.

<sup>b</sup>FT<sub>3</sub> LOD = 1.54 pmol/L. FT<sub>3</sub> concentrations were ≥LOD in 67.59% of cord blood samples.

<sup>c</sup>FT<sub>4</sub> LOD = 9.0 pmol/L. FT<sub>4</sub> concentrations were ≥LOD in 99.75% of cord blood samples.

<sup>d</sup>Among 398 subjects, maternal serum FT<sub>4</sub> and TSH concentration were able to be abstracted from medical records of 378 subjects. This information was missing in 20 subjects. FT<sub>3</sub> was not measured or recorded in medical records for all pregnant women.

All analyses were performed using the SAS 9.2 software (SAS Institute Inc., Cary, NC, USA). The level of significance was two-sided *p*-value ≤0.05.

## Results

Maternal ages ranged from 22 to 42 years with a mean of 29.8 [standard deviation (SD) 3.4] years. The majority had a college education (*n* = 331, 83.2%) or a master degree or higher (*n* = 44, 11%), and a prepregnancy BMI between 18.5 and 24.99 kg/m<sup>2</sup> (*n* = 294, 73.9%). Only one participant smoked; however, 24.6% (*n* = 98) of women confirmed passive smoke exposure (i.e., husband smoking). Among all newborns, 54% (*n* = 215) were male and 46% (*n* = 183) were female. There were 1.5% (*n* = 6) of newborns born preterm (gestation age <37 weeks). Maternal urinary TCS levels did not differ by characteristics of mothers and newborns (Table 1).

Table 2 shows the distribution of maternal urine TCS, cord blood thyroid hormone, and maternal thyroid hormone concentration at the third trimester. TCS concentrations were ≥LOD (0.1 ng/mL) in 98.24% of maternal urine samples. Additionally, a high variability in the levels of TCS was observed between the participants, with TCS concentrations ranging between LOD–89.36 ng/mL and 0.04–427.38 μg/g.Cr. This suggests a wide range of exposure doses and frequencies of TCS in this cohort. Maternal serum thyroid hormone levels were measured at 34.3 (SD, 1.2) gestational weeks at third trimester and were detectable in all women. The geometric mean (GM) of maternal serum FT<sub>4</sub> was 12.43 (SD1.36) pmol/L, and the GM of maternal serum TSH was 1.50 (0.77) mIU/L. FT<sub>3</sub> concentrations were ≥LOD (1.54 pmol/L) in 67.59% of cord blood samples, and FT<sub>4</sub> concentrations were ≥LOD (9.0 pmol/L) in 99.75% of cord blood samples. Their medians, distributions, percentiles, and ranges are described in Table 2.

Table 3 shows the associations between maternal urinary TCS concentrations (μg/g.Cr) and cord blood FT<sub>3</sub>, FT<sub>4</sub>, and TSH levels. There were no significant associations between maternal urinary TCS concentrations and cord blood FT<sub>4</sub> or TSH concentrations. However, maternal urinary TCS exhibited a significant inverse association with cord blood FT<sub>3</sub> levels. Specifically, cord blood log(FT<sub>3</sub>) concentration was 0.11 (95% CI: –0.18, –0.03) pmol/L lower in newborns of mothers with medium TCS levels compared with newborns of mothers with low TCS levels in multivariable regression models with adjustment for potential confounders (maternal age, education level, passive smoking, parity, gestational age, and prepregnancy BMI). These results were consistent when comparing high and low

**Table 3.** The associations between maternal urinary triclosan (TCS) and cord blood FT<sub>3</sub>, FT<sub>4</sub>, and TSH levels among 398 mother–infant pairs.

TCS (μg/g.Cr)	Cord blood thyroid hormone levels					
	Model 1 <sup>a</sup> β1 (95% CI)	p-Value	Model 2 <sup>b</sup> β2 (95% CI)	p-Value	Model 3 <sup>c</sup> β3 (95% CI)	p-Value
<b>LnFT<sub>3</sub> (pmol/L)</b>						
Low tertile (LOD–2.75) (n = 132)	0.55 ± 0.28		Reference		Reference	
Medium tertile (2.75–9.78) (n = 133)	0.45 ± 0.33	0.003	–0.11 (–0.18, –0.04)	0.002	–0.11 (–0.18, –0.03)	0.004
High tertile (9.78–427.38) (n = 133)	0.43 ± 0.29	0.001	–0.11 (–0.19, –0.04)	0.003	–0.11 (–0.19, –0.03)	0.004
Per unit increase in log <sub>10</sub> (TCS) (n = 398)	0.47 ± 0.30	0.02	–0.05 (–0.10, –0.01)	0.03	–0.05 (–0.10, –0.002)	0.04
Percent change in FT <sub>3</sub>	–5.82% (–9.52%, –1.00%)		–4.88% (–9.52%, –0.40%)		–4.88% (–9.52%, –0.20%)	
<b>LnFT<sub>4</sub> (pmol/L)</b>						
Low tertile (LOD–2.75) (n = 132)	2.62 ± 0.15		Reference		Reference	
Medium tertile (2.75–9.78) (n = 133)	2.63 ± 0.09	0.80	–0.007 (–0.04, 0.02)	0.63	–0.006 (–0.03, 0.02)	0.68
High tertile (9.78–427.38) (n = 133)	2.60 ± 0.12	0.38	–0.01 (–0.04, 0.02)	0.48	–0.01 (–0.04, 0.02)	0.49
Per unit increase in log <sub>10</sub> (TCS) (n = 398)	2.62 ± 0.12	0.15	–0.01 (–0.03, 0.01)	0.25	–0.01 (–0.03, 0.01)	0.27
Percent change in FT <sub>4</sub>	–1.00% (–2.96%, 1.01%)		–1.00% (–2.96%, 1.01%)		–1.00% (–2.96%, 1.01%)	
<b>LnTSH (mIU/L)</b>						
Low tertile (LOD–2.745) (n = 132)	1.71 ± 0.51		Reference		Reference	
Medium tertile (2.745–9.78) (n = 133)	1.60 ± 0.46	0.10	–0.10 (–0.22, 0.02)	0.16	–0.08 (–0.21, 0.04)	0.26
High tertile (9.78–427.38) (n = 133)	1.79 ± 0.54	0.29	0.07 (–0.06, 0.20)	0.29	0.07 (–0.06, 0.20)	0.28
Per unit increase in log <sub>10</sub> (TCS) (n = 398)	1.70 ± 0.51	0.28	0.04 (–0.03, 0.20)	0.34	0.04 (–0.04, 0.12)	0.32
Percent change in TSH <sup>d</sup>	4.08% (–2.96%, 12.75%)		4.08% (–3.92%, 11.63%)		4.08% (–3.92%, 12.75%)	

Note: FT<sub>3</sub>, free triiodothyronine; FT<sub>4</sub>, free thyroxine; LOD, limit of detection; TSH, thyroid-stimulating hormone.

<sup>a</sup>Model 1: unadjusted model.

<sup>b</sup>Model 2: adjusted for maternal age, education, passive smoking, parity, gestational age at delivery.

<sup>c</sup>Model 3: further adjusted for prepregnancy BMI categories (<18.5 kg/m<sup>2</sup>, 18.5–24.99 kg/m<sup>2</sup>, and ≥25 kg/m<sup>2</sup>).

<sup>d</sup>Percent change with 10-fold increase in maternal urinary TCS was calculated as e<sup>β</sup> – 1 \* 100, where β = coefficient from the multivariable model.

tertiles: cord blood log(FT<sub>3</sub>) was 0.11 (95% CI: –0.19, –0.03) pmol/L lower in the high tertile (*p* = 0.004). There was no difference in cord blood log(FT<sub>3</sub>) levels between medium and high tertiles of TCS groups [adjusted mean difference: 0.01 (95% CI: –0.07, 0.08) pmol/L, *p* = 0.81]. Overall, each 10-fold increase in maternal urinary TCS was associated with decreased cord FT<sub>3</sub> (percent change = –4.88%, 95% CI: –9.52, –0.20%) with adjustment for potential confounders.

Table 4 shows the associations between maternal urinary TCS concentrations (μg/g.Cr) and maternal blood FT<sub>4</sub> and TSH levels at third trimester. Maternal urinary TCS exhibited a significant inverse association with maternal blood FT<sub>4</sub> and TSH. Specifically, high tertile of urinary TCS concentrations was associated with 0.03 lower in maternal log(FT<sub>4</sub>) pmol/L (95% CI –0.06, –0.006) in the adjusted model. With each 10-fold increase in maternal urinary TCS, maternal blood FT<sub>4</sub> was 1.98% lower (95% CI: –3.92%, –0.10%) with adjustment for potential confounders. The medium tertile of maternal urinary TCS concentration was associated with 0.15 lower level of maternal blood log(TSH) mIU/L (95% CI: –0.28, –0.03) with adjustment for covariates at third trimester. However, when comparing high and low tertiles, the differences of maternal log(TSH) were not statistically significant (*p* > 0.05).

No statistically significant associations were observed between maternal TCS exposure and positive maternal or cord blood TPOAb (≥5.61 IU/mL) in any of our analyses (Table 5).

## Discussion

Thyroid homeostasis undergoes significant physiologic changes during pregnancy, and therefore is potentially sensitive and vulnerable to environmental disruptors such as TCS exposure. Our study is the first to explore the relationship between prenatal TCS exposure and maternal and neonatal thyroid hormone levels in a birth cohort. We found evidence of inverse associations between maternal TCS exposure and maternal FT<sub>4</sub> and neonatal FT<sub>3</sub> levels. A medium maternal urinary TCS level was associated with lower maternal TSH concentrations at third trimester, but this relationship was not found in the high urinary TCS level group. No association was found between maternal TCS exposure and positive TPOAb in either maternal or cord blood.

Evidences from animal experiments suggest that TCS exposure have negative association with T<sub>4</sub> (Crofton et al. 2007; Paul et al. 2010) and T<sub>3</sub> (Paul et al. 2010) in rats, and reduced T<sub>4</sub> in pregnant rats (Axelstad et al. 2013). In another study, plasma T<sub>3</sub> and T<sub>4</sub> levels were not affected by TCS exposure in *Xenopus laevis* (Fort et al. 2010). However, contrary to the Fort claims, others believed that they provided the evidence of thyroid axis disruption by TCS (Veldhoen et al. 2006).

There was no previous study that examined this topic among pregnant women. Among nonpregnant population, previous studies yielded conflicting results on the association between TCS exposure and thyroid hormone levels. Two studies indicated that the use of TCS-containing toothpaste might not alter thyroid function in nonpregnant population. In one of the studies, there were no identified significant associations between exposure of TCS-containing toothpaste and thyroid hormone among 12 healthy adult volunteers (Allmyr et al. 2009). In the other study, among 132 cardiovascular patients with an average age of 62 years, no evidence of detected changes in blood thyroid hormone in TCS exposed individuals was found (Cullinan et al. 2012). For the first of the two studies, the findings could be due to the small sample size and short exposure duration; for the second study, the findings could be due to the lack of data on the use of other TCS products and objective measurements of plasma or urinary TCS concentrations among the participants. However,

**Table 4.** The associations between maternal urinary triclosan (TCS) and maternal FT<sub>4</sub> and TSH level at the third trimester among 378 pregnant women.

TCS (μg/g.Cr)	Maternal thyroid hormone levels at third trimester					
	Model 1 <sup>a</sup> β1 (95% CI)	p-Value	Model 2 <sup>b</sup> β2 (95% CI)	p-Value	Model 3 <sup>c</sup> β3 (95% CI)	p-Value
LnFT <sub>4</sub> (pmol/L)						
Low tertile (LOD–2.72) (n = 126)	2.53 ± 0.11	0.89	Reference	0.76	Reference	0.89
Medium tertile (2.72–9.64) (n = 126)	2.53 ± 0.10	0.02	0.004 (–0.02, 0.03)	0.03	0.002 (–0.03, 0.03)	0.02
High tertile (9.64–427.38) (n = 126)	2.50 ± 0.11	0.06	–0.03 (–0.06, –0.01)	0.05	–0.03 (–0.06, –0.006)	0.03
Per unit increase in Log <sub>10</sub> (TCS) (n = 378)	2.52 ± 0.11		–0.02 (–0.03, –0.001)		–0.02 (–0.04, –0.001)	
Percent change in FT <sub>4</sub>			–1.98% (–2.96%, –0.10%)		–1.98% (–3.92%, –0.10%)	
LnTSH(mIU/L)						
Low tertile (LOD–2.72) (n = 126)	0.47 ± 0.47	0.02	Reference	0.02	Reference	0.02
Medium tertile (2.72–9.64) (n = 126)	0.33 ± 0.49	0.50	–0.14 (–0.27, –0.02)	0.51	–0.15 (–0.28, –0.03)	0.45
High tertile (9.64–427.38) (n = 126)	0.43 ± 0.51	0.72	–0.04 (–0.16, 0.08)	0.76	–0.05 (–0.17, 0.08)	0.70
Per unit increase in Log <sub>10</sub> (TCS) (n = 378)	0.41 ± 0.49		–0.01 (–0.10, 0.06)		–0.02 (–0.10, 0.06)	
Percent change in TSH <sup>d</sup>			–1.00% (–9.52%, 6.18%)		–1.98% (–9.52%, 6.18%)	

Note: FT<sub>3</sub>, free triiodothyronine; FT<sub>4</sub>, free thyroxine; LOD, limit of detection; TSH, thyroid-stimulating hormone.

<sup>a</sup>Model 1: unadjusted model.

<sup>b</sup>Model 2: adjusted for maternal age, education, passive smoking, parity, gestational age at which maternal thyroid hormones were measured.

<sup>c</sup>Model 3: further adjusted for pregnancy BMI categories (<18.5 kg/m<sup>2</sup>, 18.5–24.99 kg/m<sup>2</sup>, and ≥25 kg/m<sup>2</sup>).

<sup>d</sup>Percent change with 10-fold increase in maternal urinary TCS was calculated as e<sup>β</sup> – 1 \* 100, where β = coefficient from the multivariable model.

another study revealed a negative association between urinary TCS and blood FT<sub>4</sub> levels in obese women (Geens et al. 2015). In contrast, a positive association was observed between TCS and total T<sub>3</sub> concentrations in adolescents from NHAHES data (Koeppel et al. 2013).

When comparing the geometric mean of this study to other studies, the TCS exposure of our cohort fell within the medium level. The geometric mean of maternal urinary TCS concentration was 2.87 ng/mL in this study, which was higher than previous studies of pregnant women in Norway (<2.3 ng/mL) (Bertelsen et al. 2014), and Denmark (<1.21 ng/mL) (Frederiksen et al. 2014), but lower than cohorts from Canada (12.64 ng/mL) (Arbuckle et al. 2015), the United States (13.8 ng/mL) (LaRocca et al. 2014), and the U.S. NHANES (17 ng/mL) (Woodruff et al. 2011).

Currently, there are no clinical normal ranges for cord serum levels of FT<sub>3</sub>, FT<sub>4</sub>, and TSH yet in China. The levels of cord blood thyroid hormone in this study were similar to what were reported in previous Chinese studies (Liang et al. 2002; Wang and Xu 2002). For example, one study demonstrated that the mean ± SD of cord serum FT<sub>3</sub> was 2.06 ± 0.60 pmol/L, FT<sub>4</sub> was 13.94 ± 2.65 pmol/L and TSH was 7.86 ± 3.81 mIU/L, respectively, by screening 1,121 newborns in China in 2001 using electrochemiluminescent microparticle immunoassays in the Beckman Architect system (Liang et al. 2002). In our study, the geometric mean of FT<sub>3</sub> was 1.61 ± 0.35 pmol/L, FT<sub>4</sub> was 13.70 ± 1.47 pmol/L and TSH was 5.49 ± 4.73 mIU/L measured by chemiluminescent microparticle immunoassay using the Architect system.

In this study, a significant inverse association was found between maternal urinary TCS and cord blood FT<sub>3</sub> as well as maternal blood FT<sub>4</sub> concentrations at third trimester. Although how TCS disrupts thyroid hormones is still unclear, our findings are biologically plausible based on evidence from animal studies concluding that TCS had the potential to influence thyroid function by changing the activity of glucuronyltransferase in Phase II (the reaction of conjugations) in the liver (Schoor et al. 1998; Wang et al. 2004). The glucuronidation in Phase II is the key step for T<sub>4</sub> inactivation. Therefore the decreased T<sub>4</sub> level may result from increased T<sub>4</sub> clearance through activating enzymes. Another study suggests that TCS exposure leads to hypothyroxinemia via increased hepatic catabolism (Paul et al. 2010). However, we noted that TCS is a low efficient thyroid hormone disruptor that manifests mild effects on thyroid hormone metabolism. In addition, it is uncertain whether the mechanisms by which thyroid disruption occurs in rats are the same in humans.

In terms of the inverse association between medium maternal urine TCS levels and maternal blood TSH concentrations, we speculate that a medium level of TCS may inhibit TSH secretion by acting as negative feedback to the hypothalamic-pituitary-thyroid axis based on the similar structure of TCS and T<sub>4</sub>. However, the inverse association for maternal blood TSH was not observed when comparing high and low maternal urine TCS levels. Due to the scarcity of relevant mechanism studies, the interpretation of these results needs to be unfolded with additional studies.

As previously stated, TCS is a liposoluble substance, and can be detected in the umbilical cord blood of newborns with the serum concentration of TCS ranged from 0.5 to 5.0 ng/g (Peters 2005), which indicates that TCS can be transferred through the placenta from mothers to fetuses during pregnancy. The thyroid hormone alternations associated with TCS exposure differ between pregnant women and newborns in this study. Differences in metabolism, distribution kinetics, and other susceptibility factors between mother and fetus might contribute to

**Table 5.** Multiple logistic regression on the associations between maternal urinary triclosan (TCS) and maternal and neonatal thyroid peroxidase antibody (TPOAb).

TCS ( $\mu\text{g/g Cr}$ )	Cord blood TPOAb					
	Model 1 <sup>a</sup> OR (95% CI)	<i>p</i> -Value	Model 2 <sup>b</sup> OR(95% CI)	<i>p</i> -Value	Model 3 <sup>c</sup> OR (95% CI)	<i>p</i> -Value
Low tertile (LOD–2.745) ( <i>n</i> = 132)	Reference		Reference		Reference	
Medium tertile (2.745–9.78) ( <i>n</i> = 133)	0.65 (0.28, 1.49)	0.31	0.65 (0.27, 1.53)	0.32	0.67 (0.28, 1.59)	0.36
High tertile (9.78–427.38) ( <i>n</i> = 133)	0.57 (0.24, 1.36)	0.20	0.59 (0.25, 1.43)	0.24	0.60 (0.25, 1.46)	0.26
Per unit increase in log(TCS) ( <i>n</i> = 398)	0.98 (0.78, 1.23)	0.84	0.98 (0.77, 1.24)	0.84	0.98 (0.77, 1.24)	0.86

  

TCS ( $\mu\text{g/g Cr}$ )	Maternal TPOAb					
	Model 1 <sup>a</sup> OR (95% CI)	<i>p</i> -Value	Model 2 <sup>b</sup> OR(95% CI)	<i>p</i> -Value	Model 3 <sup>c</sup> OR (95% CI)	<i>p</i> -Value
Low tertile (LOD–2.72) ( <i>n</i> = 126)	Reference		Reference		Reference	
Medium tertile (2.72–9.64) ( <i>n</i> = 126)	1.18 (0.53, 2.58)	0.69	1.09 (0.49, 2.44)	0.84	1.06 (0.47, 2.39)	0.89
High tertile (9.64–427.38) ( <i>n</i> = 126)	1.32 (0.59, 2.94)	0.50	1.26 (0.56, 2.85)	0.58	1.22 (0.53, 2.79)	0.63
Per unit increase in log(TCS) ( <i>n</i> = 378)	1.01 (0.81, 1.26)	0.94	1.03 (0.83, 1.28)	0.78	1.03 (0.83, 1.27)	0.81

Note: FT<sub>3</sub>, free triiodothyronine; FT<sub>4</sub>, free thyroxine; LOD, limit of detection; TSH, thyroid-stimulating hormone.

<sup>a</sup>Model 1: unadjusted model.

<sup>b</sup>Model 2: adjusted for maternal age, education, passive smoking, parity, gestational age at delivery.

<sup>c</sup>Model 3: further adjusted for prepregnancy BMI categories (<18.5 kg/m<sup>2</sup>, 18.5–24.99 kg/m<sup>2</sup> and  $\geq$ 25 kg/m<sup>2</sup>).

<sup>d</sup>Model 2: adjusted for maternal age, education, passive smoking, parity, gestational age at which maternal thyroid hormones were measured.

the results (Frederiksen 2001). It could also be due to differences in exposure levels of TCS between mother and fetus during gestation. In addition, the process of transferring thyroid hormones from mother to fetus might be another possible mechanism of the observed differences (Vulsma et al. 1989).

Our study has several advantages. First, a prospective birth cohort design was used to evaluate the association between maternal TCS exposure and thyroid hormone levels in newborns. Second, gestational thyroid disease diagnosis was based on integrated data during the whole pregnancy by professional physicians and an in-depth analysis after excluding women with gestational hyperthyroidism, hypothyroidism, or subclinical hypothyroidism was performed. Finally, due to the large range of maternal urinary TCS levels, this study from 398 mother–infant pairs afforded us decent power to detect small-scale associations.

Our study also has limitations. First, due to an observational and cross-sectional study for maternal thyroid hormone analysis, we cannot establish the causality. These findings need to be substantiated through further research. Second, we assessed urinary levels of TCS from the urine at a single time point late in pregnancy. However, a recent study evaluating the reliability of TCS measures in repeated urine samples from Norwegian pregnant women reported that the repeated measures of urinary TCS concentration (at 17, 23, and 29 weeks of gestation) on the same woman were correlated. The intraclass correlation coefficient (ICC) was 0.49, indicating moderate reproducibility (Bertelsen et al. 2014). Another recent study reported that a single spot urine sample can be used to accurately predict an individual's overall geometric mean TCS concentration corresponding to low, medium, or high exposure. The overall prediction accuracy was 86.7% (Weiss et al. 2015). In our analysis, we have also categorized maternal TCS concentrations in tertiles. In addition, any misclassification of TCS exposure levels, if existed, is most likely to be nondifferential, which may have drawn the association results toward the null. Third, we did not collect the information on the use of personal care products, which would have been helpful in trying to ascertain routes of exposure and to potentially explain the wide range of TCS values. However, lack of this information has no impact on our key study objectives and conclusions. Finally, other confounders, which may affect thyroid hormone levels, were not measured, including iodine intake or urinary iodine concentrations and other environmental compounds. However, iodine is fortified in salt in China (Shi et al. 2015), and we excluded those women with thyroid disease before

or during pregnancy in this report. The results of this study were less likely to be biased by the iodine deficiency.

In summary, we observed a significant inverse association between maternal urinary TCS and cord blood FT<sub>3</sub> as well as maternal blood FT<sub>4</sub> and TSH concentrations at third trimester. Future study is needed to examine whether TCS exposure during perinatal period, a highly sensitive window, may profoundly affect child neurobehavioral development.

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