

Iodine metabolism and thyroid function during the perinatal period: Maternal-neonatal correlation and effects of topical povidone-iodine skin disinfectants

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Abstract

An adequate maternal iodine intake during pregnancy and lactation is essential for growth and mental development in fetuses and newborns. Both deficient and excess iodine may disrupt normal thyroid function. There are limited data on perinatal iodine metabolism in mothers and infants, as well as the effect of povidone-iodine (PVP-I) antiseptics used in Cesarean delivery. The urinary iodine concentration (UIC), serum iodine, thyrotropin (TSH), free thyroxine (FT4) and breast milk iodine concentration (BMIC) were measured consecutively in a total of 327 mothers and 249 term-infants in two prospective studies. The maternal median UIC was 164 µg/L in the third trimester, increased to 256 µg/L on postpartum day 2, then decreased to 116 µg/L one month later. The BMIC on postpartum days 2 and 30 was 17.6 and 13.5 µg/100g, respectively. In neonatal infants born to the mothers unexposed to PVP-I, the median UIC was 131 µg/L in the first voiding urine and increased to 272 µg/L on day 4, then slightly decreased to 265 µg/L on day 28 suggesting sufficient iodine reserve at birth. PVP-I antiseptics containing 1g of iodine for skin preparation at Cesarean delivery transiently increase maternal serum iodine concentration, UIC and BMIC, however, it has little effect on maternal TSH, FT4 and neonatal UIC, TSH, or FT4. The iodine status of pregnant women and their infants was adequate in this population; however, the UIC in lactating mothers at one postnatal month was low enough to suggest iodine deficiency or near iodine deficiency. Further studies are necessary.

This study was not registered to any clinical trials registry (CTR).

Introduction

Iodine is an essential component of thyroid hormone, and maternal dietary iodine deficiency results in growth and mental impairment in fetuses, newborns and infants [1–4]. According to a report by the United Nations Children’s Fund (UNICEF) in 2018 nearly 19 million babies are born globally every year and 14 per cent are at risk of permanent yet preventable brain damage and reduced cognitive function due to a lack of iodine in the earliest years of life [5]. The neurodevelopmental defects are a direct consequence of a lack of thyroid hormone during critical stages of fetal development, and the supply of adequate quantities of thyroid hormone depends on maternal transfer of the hormone across the placenta, especially during the first two trimesters of pregnancy until the fetal thyroid gland is functioning [4, 6]. Thyroid hormone and iodine requirements increase from early gestation to term because of 1) an increase in maternal thyroxine (T4) production to maintain maternal euthyroid status and transfer thyroid hormone to the fetus early in the first trimester; 2) to transfer iodine to the fetus, particularly in later gestation; and 3) to cover probable increased renal iodine loss during pregnancy [1, 7, 8].

Brain development continues postnatally and adequate production of thyroid hormone in infancy is critical for the continuation of somatic and brain growth and development because thyroid hormone requirements are greatest per kg of body weight in infancy than at any other life stage [8]. The supply of iodine to the infant comes from breast milk that is dependent on the dietary iodine intake of the mother, and an adequate supply of iodine to the exclusively breast-fed infant is essential during lactation. The

World Health Organization (WHO) has recommended the consumption of 250 µg of iodine per day for pregnant and lactating women [9].

In the perinatal period, which is traditionally defined as from about 24 weeks of pregnancy up to either 7 or 28 days of life, there are remarkable changes in thyroid function and iodine metabolism as well as cardiovascular, renal and endocrine function. In addition, iatrogenic iodine overload in fetal and neonatal life, caused by either iodine disinfection agents, povidone-iodine (PVP-I), or contrast medium during the perinatal period, may block iodine uptake by the thyroid gland and inhibit hormone synthesis (Wolff-Chaikoff effect), resulting in transient neonatal hypothyroidism or hyperthyrotropinemia [10].

There are few data on maternal-fetal iodine metabolism during this short period in iodine-sufficient areas. The purpose of this study is to characterize 1) the changes of iodine concentration in urine, serum and breast milk as well as thyroid function in mothers and infants before and after birth, and 2) the effects of iodine exposure by antiseptics on maternal and fetal iodine metabolism and thyroid function in the early postnatal period.

Materials And Methods

Study subjects

Two prospective studies were consecutively conducted in two maternal clinics located in Yokohama City, Japan between July 2010 and October 2014. The distance between the two clinics was approximately 13 miles. Healthy pregnant women who consecutively attended and were without a known history of thyroid dysfunction or taking thyroid hormone or anti-thyroid drugs, and their newborn infants were randomly recruited in the study. The first study (Study 1) was conducted from July 2010 to October 2011 in Ogawa Clinic and 149 mothers and 146 infants were included. The second study (Study 2) was conducted again in Ogawa Clinic from October to December 2013 and in Nakamachidai Ladies Clinic from March to October 2014 in the same way. After excluding the subjects with severe obstetric complications and high serum thyroid autoantibody (ThAb) values or the infants with perinatal complications, a total of 178 mother–infant pairs, 103 from Ogawa Clinic and 75 from Nakamachidai Ladies Clinic, were combined together because there was no statistically significant difference in the mother's age, body weight, height and dietary iodine intake (DII) as well as the infant's gestational age, birth weight, height, male to female ratio and thyroid function (Table 1). Gestational dates were confirmed by ultrasound in the first trimester of pregnancy. A total number of 327 mothers and their 324 of their infants were included in the studies. Seventy-five of 327 women were delivered by Caesarean section due to various obstetric complications. Cesarean section delivery includes both elective and emergent Caesarean delivery and these two subtypes were not differentiated in this study.

Iodine-containing disinfectants were not used routinely in the maternal and neonatal unit. The type of disinfectant employed for perineal preparations prior to deliveries was 0.025% benzalkonium chloride (BZC), while during Caesarean deliveries 10% povidone-iodine (PVP-I), *i.e.*, ISODINE® solution 10%,

Shionogi Healthcare Co., Ltd. Osaka, Japan (distributor) and Mundipharma K.K., Tokyo, Japan (manufacturer) was used for abdominal skin sterilization which is distributed as BETADINE® outside Japan. The skin in the lower abdomen was swabbed three times by using cotton balls presoaked with exactly 100 mL of 10% PVP–I solution which contains 1g of effective iodine. To avoid prolonged contact with PVP–I, after it dried, the skin was wiped off with a sodium thiosulfate-ethanol swab until all of the color from the iodine had disappeared. The time from applying PVP–I solution on the mother's skin to cutting off the umbilical cord of the newborn infant was usually 10 minutes.

Based on the type of disinfectant used prior to delivery, all subjects including the neonatal infants were divided into two groups, *i.e.*, Cesarean section delivery with prepared povidone-iodine application for abdominal preparation (CS–PVP–I group) and vaginal delivery prepared with benzalkonium chloride (VGD–BZC group) (Table 1), and the parameters of iodine status and thyroid function were compared between the two groups. The mothers and infants who were not exposed to iodine-containing disinfectant and serially provided four urine samples were included in a longitudinal study on perinatal change of urinary iodine excretion.

Sampling for analyses

In Study 1, a total of four spot urine samples for determining urinary iodine concentration (UIC) were collected from the pregnant women at the 28–37th week of gestation, during the active phase of the delivery, on day 2 after delivery, and the first month after delivery. Venous blood samples were obtained together with the first and third urine samples and serum thyrotropin (TSH), free thyroxine (FT4) and iodine concentrations were measured. Three serum ThAbs, *i.e.*, TSH receptor antibody (TRAb), thyroperoxidase antibody (TPOAb) or thyroglobulin antibody (TgAb) were exclusively measured, when their TSH and/or FT4 values in the samples obtained at the initial study visit were out of the reference range. Neonatal urine was collected using a small self-adhesive sterile bag (Atom Medical, Tokyo Japan) during the first 24 h, on day 4 or 5 and at 28 days after birth. A nurse placed a bag on the perineum of the infants at birth and checked every 2 hours until the first voiding, and then 2 mL of clean urine not soiled by feces was collected using a 5 mL disposable syringe. The last urine sample of infants was collected at home using a plastic bag by each of the infants' mothers within 24 h before her postpartum visit to the clinic and kept refrigerated.

In Study 2, urine and breast milk samples were collected from the lactating mothers on day 4 and one month after birth. Breast milk samples were obtained by manual expression and stored at –20 °C.

As part of the National Neonatal Screening Program a heel-prick blood sample was taken on filter paper on postnatal day 5 from all infants in both studies, and TSH, FT4 concentrations were measured. All serum and urine samples were kept frozen at –30 °C before analysis.

Calculation of dietary iodine intake and urinary iodine excretion for mothers and infants

Maternal dietary iodine intake (DII) was assessed before and after delivery by using a semi-quantitative food frequency questionnaire (FFQ). The daily DII from each food was calculated on the basis of daily, weekly or monthly frequency of food consumption and iodine content of the specific food and given in μg iodine per day [11].

Newborn infants were fed with 10 ml of 5% glucose at 6 to 8 h after birth, followed by 10 ml of breast milk or formula milk increasing the amount every three hours thereafter. Each infant's feeding status (type and ratio of breast milk) was obtained from interviews with their mothers at the infant checkup on day 2 and one month after birth. The daily DII in infants during the early neonatal period was calculated with his or her own mother's breast milk iodine concentration (BMIC) and the sucked amount of breast milk or formula milk by weighing the infant's body weight before and after feeding. The formula milk used in the two hospitals is the same product, "Hohoemi", Meiji Co., Ltd., Tokyo. We have measured the iodine content in this milk and the mean iodine concentration was $51.35\mu\text{g}/100\text{g}$. The most reliable method to evaluate urinary iodine excretion (UIE) is a 24-h collection of urine, however, in this study the estimated 24-h UIE of infants was calculated based on the UIC in single specimens, assuming a daily urine volume in neonatal infants of 90 or 250 mL according to a previous report on Asian term-infants [12].

Analytical methods

Serum TSH and FT4 were measured by electrochemiluminescence immunoassay (ECLIA) using ECLusys TSH and FT4 (Roche Diagnostics K.K., Tokyo, Japan). The detection limit and reference ranges for Japanese given by the manufacturers were: TSH, 0.005 mIU/L, 0.50–5.0 mIU/L; FT4, 0.01 ng/dL, 0.90–1.70 ng/dL. TRAb, TPOAb and TgAb in maternal serum were measured by ECLIA using ECLusys TRAb, ECLusys TPOAb and ECLusys TgAb (Roche Diagnostics K.K., Tokyo, Japan), respectively. Serum ThAbs values above the manufacturer's reference limit (2.0 IU/L for TRAb, 16 IU/mL for TPOAb and 28 IU/mL for TgAb) were considered positive. Neonatal blood TSH, and FT4 were measured in the dried heel blood spot samples by enzyme-linked immunosorbent assay (ELISA) using Cretin TSH ELISA II 'Eiken' (Eiken Chemical Co., Ltd. Tokyo, Japan) and Enzaplate N-FT4 (Siemens Healthcare Diagnostics Inc. Tokyo, Japan), respectively. The detection ranges were: TSH, 0.5–100.0 mIU/L; FT4, 0.20–10.0 ng/mL. The intra-assay and inter-assay coefficients of variation for TSH were 5.9–7.7% and 6.2–7.9%, respectively. The intra-assay and inter-assay coefficients of variation for FT4 were 4.11–5.29% and 4.21–5.47%, respectively.

The iodine concentration of serum and urine samples was measured at Hitachi Chemical Co., Ltd., Kawasaki, Japan using the modified microplate method based on the ammonium persulfate digestion on microplate (APDM) method with spectrophotometric detection of the Sandell-Kolthoff reaction [13]. The analytical sensitivity for iodine was $13.9\mu\text{g}/\text{L}$ and the intra-assay and inter-assay coefficients of variation were 1.8–6.3 and 1.5–6.9%, respectively. This laboratory is controlled by its participation in the Ensuring the Quality of Urinary Iodine Procedures (EQUIP) program of the Centers for Disease Control and Prevention, Atlanta, U.S.A. [14]. The creatinine (Cr) concentration in urine was estimated by colorimetric enzymatic assay.

Breast milk samples were sonicated for 15 min in a 37 °C water bath by using Ultrasonic Cleaner, ASU-20, AS ONE Corporation—Osaka, Japan (oscillation frequency: 40 kHz, high frequency output power: 360W). Iodine in breast milk was extracted and measured in accordance with “The official method for determining the iodine content of foods” published by Minister of Health, Labour and Welfare, Japan [15]. Five hundred microliters of the sample solution were weighed using a precision balance with the minimum display of 0.1–0.01 mg, Shimadzu AUW120D, Shimadzu Corporation, Kyoto, Japan, and added to a polypropylene tube (DigiTUBE[®], GL Sciences, Tokyo, Japan) up to a volume of 50 mL with 0.5% TMAH solution for extraction at 60 °C for 12 h. After cooling to room temperature, the suspension was centrifuged by 3,000 rpm for 10 min, then 15 mL of the supernatant was collected, and stored at –70°C until analysis. The total iodine content was determined by using inductively coupled plasma-mass spectrometry (ICP–MS), iCAP Q (serial # ICAPQ 01668) with Cetac ASX260, Thermo Fisher Scientific K.K., Tokyo, Japan. The limit of detection (LOD) and background equivalent concentration (BEC) of this assay were 0.005 and 0.187 ppb, respectively. The intra-assay coefficient of variation was 5%. All analytical procedures were carried out at the Central Laboratory, Teikyo University, Tokyo, Japan.

Ultrapure water was prepared using a pure water production system for laboratory analysis, PURELAB Ultra Ionic, Organo Corporation, Tokyo, Japan, with a specific electrical resistance value of 18.2MΩ·cm at 25 °C. The reagents used were: 25% tetramethyl ammonium hydroxide solution (TMAH), Wako Pure Chemical Industries, Ltd., Japan; Certified reference material for iodine, AS–I9–2Y 1,000 µg/mL Iodide (Lot No. 4–25I–2Y) SPEX CertiPrep, LLC. NJ, U.S.A.; Calibration standard for ICP-MS as internal standard solution, Tellurium (Te), 1,000 µg/mL and Indium (In), 1,000 µg/mL, SCP Science, Canada. The standard reference materials for non-fortified human milk, SRM 1953 (Iodine: 193±2 mg/Kg), the National Institute of Standards and Technology (NIST), U.S.A. was used for analytic quality control.

All samples were assayed in duplicate. BMIC was expressed as µg/100g. UIC was expressed relative to creatinine excretion (UI/Cr, µg/gCr) or as a concentration (µg/L, 1µg/L=0.00788 nmol/L for conversion to S.I. units). In newborn infants UI/Cr was not used since it is reported that in the first week of life the UI/Cr value in a spot urine sample is highly variable and not useful to standardize iodine excretion of newborn infants [16].

Statistics

The results were presented as median, range, percentile or mean with SD. The UIC, UI/Cr, BMIC, DII, serum iodine, serum or blood TSH and FT4 concentrations were not normally distributed. Differences between paired data or groups were examined using one-way analysis of variance (ANOVA) with Friedman’s Multiple Comparison Test. Differences between two unmatched groups for normally and non-normally distributed data were tested using the unpaired t test and Mann-Whitney test, respectively. A P-value less than 0.05 was considered as “statistically significant”. All data were processed and statistically analyzed using GraphPad Prism version 8 (GraphPad Software, San Diego, CA, U.S.A.).

Epidemiological criteria of iodine status in pregnant and lactating women and children

The median UIC expressed as micrograms of iodine per liter ($\mu\text{g/L}$) is used for better comparison of the population's iodine status with the WHO-defined deficiency grades. The iodine intake in pregnant, lactating women and infants is regarded as follows: insufficient, below $150 \mu\text{g/L}$; adequate, 150 to $249 \mu\text{g/L}$; more than adequate, 250 to $499 \mu\text{g/L}$; excessive, $500 \mu\text{g/L}$ or higher for pregnant women and insufficient, below $100 \mu\text{g/L}$; adequate, $100 \mu\text{g/L}$ or higher for both lactating women and infants less than two years old.

Results

Iodine status and changes in thyroid function of pregnant women and newborn infants by a cross sectional study

In Study 1, the median value of UIC in the third trimester (32.2 ± 1.3 weeks gestation) was 164 (IQR: 91 , 300) $\mu\text{g/L}$ and increased to $256 \mu\text{g/L}$ at 2–3 days after delivery, then decreased to $116 \mu\text{g/L}$ at one month. The median UI/Cr values also showed similar changes as UIC (Table 1). In Study 2, the median UIC after delivery was $101 \mu\text{g/L}$ and decreased to $86 \mu\text{g/L}$ at one month which were lower than those in Study 1. The median DII estimated in the third trimester was $369 \mu\text{g/day}$ and decreased to $276 \mu\text{g/day}$ one month after delivery in Study 1, while in Study 2, the DII increased from 346 to $381 \mu\text{g/day}$ (Table 1). When combining all the lactating subjects in the two studies together, the median (IQR) UIC was 138 (86 , 256) $\mu\text{g/L}$ at 2–3 days after delivery ($n=314$) and 107 (58 , 217) $\mu\text{g/L}$ at one month ($n=206$). The median DII was $356 \mu\text{g/day}$ in the third trimester and $301 \mu\text{g/day}$ at one postpartum month without significant difference.

The median values of maternal serum iodine and TSH concentrations increased after birth (12.3 vs. $14.9 \mu\text{g/L}$, $p=0.0002$ for iodine; 0.75 vs. 1.55 mIU/L , $p<0.0001$ for TSH at 2.0 ± 0.1 days), while serum FT4 levels remained unchanged. Since the serum TSH and/or FT4 values in 37 pregnant women were out of the reference range, TRAb was measured in 28 subjects and there were no positive subjects, while TPOAb and TgAb were measured in 9 subjects, and positive values were observed in 7 and 3 subjects, respectively. As a result, 6 of 149 subjects (4.0%) were diagnosed as having subclinical hypothyroidism.

The median (IQR) UIC of the infant's urine samples in the first voiding ($n=146$), at 4 ($n=139$) and 28 ($n=103$) days after birth were 109 (62 , 178), 277 (173 , 449) and 256 (121 , 495) $\mu\text{g/L}$, respectively indicating a rapid increase of iodine concentration. The median UIC value in the infants nursed with breast milk for more than 50% of total feedings ($n=61$) was significantly higher than that of the other infants ($n=25$), (293 vs. $196 \mu\text{g/L}$, $P=0.0155$). Median blood TSH and FT4 values in neonatal heel blood were within the reference range and there was no infant diagnosed as being congenitally hypothyroid in both Studies 1 and 2 (Table 1).

Perinatal change of UIC, UI/Cr and Cr concentration in pregnant women, postpartum women and infants by a repeated measurement in Study 1

After excluding the subjects who were exposed to iodine-containing disinfectants at delivery (*i.e.*, the CS–PVP–I group) the change of urinary iodine and Cr excretion was observed in 90 mothers and their 77 of their infants who provided complete urine samples as a longitudinal study. The median UIC and UI/Cr values in the third trimester and one day before delivery were 139 µg/L or 220 µg/gCr and 158 µg/L or 226 µg/gCr, respectively, and then increased to 216 µg/L or 212 µg/gCr on day 2 after birth. At postpartum day 29 the median UIC and UI/Cr values decreased to 102 µg/L or 145 µg/gCr, respectively, and were significantly lower than those before delivery (Fig. 1).

A similar change was observed in urinary creatinine concentration. However, there was no significant difference in the UI/Cr value before and after birth, while UIC and urinary Cr concentration increased markedly after birth (Table 2).

In the neonatal infants the median UIC value in the first voiding urine was 131 µg/L and increased to 272 µg/L on day 4, then slightly decreased to 265 µg/L on day 28 (Fig. 2). At the same time median urinary Cr concentration decreased by age (Table 3).

Correlation between maternal and neonatal UICs in Study 1

Neonatal UIC in the first voiding urine was significantly but weakly correlated with maternal UIC, *e.g.*, in the third trimester (Pearson $r=0.2002$, $p=0.0178$), at 12.6 hours before birth (Pearson $r=0.2163$, $p=0.009$) and on postpartum day 29 (Pearson $r=0.2104$, $p=0.012$). Neonatal UIC on postnatal day 28 also weakly correlated with maternal UIC before birth (Pearson $r=0.2504$, $p=0.0167$) and postpartum day 29 (Pearson $r=0.2765$, $p=0.0064$). There was no significant correlation of maternal UI/Cr with neonatal UIC. In addition, the median UIC in the formula-fed infants was significantly lower than that in breast-fed infants at one month (median: 108.0 vs. 246.0µg/L).

Correlation between neonatal UICs and blood TSH or FT4 in Study 1

The neonatal blood TSH and FT4 concentrations were not significantly correlated with neonatal UICs on day 1 (Spearman $r=-0.1295$, $p=0.1218$ for TSH, Spearman $r=0.02923$, $p=0.728$ for FT4, $n=144$) or day 4 (Spearman $r=-0.007446$, $p=0.9307$ for TSH, Spearman $r=0.01415$, $p=0.8687$ for FT4, $n=139$). When neonatal urine samples were divided into two groups according to UIC with a cut-off value of 100 µg/L, the mean neonatal TSH and FT4 values in the group <100 µg/L on day 1 ($n=68$) were not significantly different from those in the UIC group >100 µg/L ($n=76$), (3.21 vs. 2.85 mIU/L for TSH, 1.68 vs. 1.72 ng/dL for FT4). The same result was observed between UIC on day 4 and TSH or FT4.

Changes in breast milk iodine concentration and iodine intake in neonatal infants during the early neonatal period in Study 2

Breast milk samples were obtained at 4.0 (1.6) and 33.1 (4.3) of mean (SD) days from 178 lactating women in two hospitals. Since there was statistically no difference in BMIC between the two hospitals, all the data was combined. The BMIC was highly variable and the median (2.5 and 97.5% percentile) value

was 17.6 (11.1, 35.5) $\mu\text{g}/100\text{g}$ in the early postpartum period and 13.5 (8.2, 23.8) $\mu\text{g}/100\text{g}$ at one postpartum month. The BMIC in the lactating mothers who were not exposed to iodine-containing disinfectants was positively correlated with maternal UIC and UI/Cr in early postpartum period (Fig. 3, Panel A and B) and at one postpartum month (Fig. 3, Panel C and D).

In neonatal infants the estimated 24 h DII calculated with the sucked amount and iodine content of milk increased from almost zero at day 0 to 35.7 $\mu\text{g}/24\text{h}$ at day 4 with the increasing feeding rate while the estimated 24 h UIE was 8.8 $\mu\text{g}/24\text{h}$ at day 0 and 60.8 $\mu\text{g}/24\text{h}$ at day 4 suggesting a negative iodine balance during the early neonatal period (Table 4).

The effects of maternal topical povidone- iodine exposure on iodine metabolism and thyroid function in mothers and their neonates

In Study 1, there was no difference in maternal age, height, weight, parity, infants' height, weight and male/female ratio except for the gestational period between the CS-PVP-I group and the VGD-BZC group (Table 5). Between the two groups the median UIC, UI/Cr, serum TSH, FT4 and total iodine concentrations were not significantly different in the third trimester and the median UIC and UI/Cr were also not different several hours before delivery; however, on postpartum day 3, *i.e.*, 36–56 h after delivery, the median UIC, UI/Cr and total serum iodine concentrations in the CS-PVP-I group were 6.4, 4.9 and 1.8 times greater than those in the VGD-BZC group, respectively. In addition, the postsurgical UIC value was markedly increased compared to the preoperative UIC value (median UIC, 179 *vs.* 1,430 $\mu\text{g}/\text{L}$). The serum TSH value in the CS-PVP-I group was significantly lower than that in the VGD-BZC group although the *p* value was 0.045 and barely reached statistical significance while there was no difference in serum FT4 value between the two groups. At postpartum day 29 the UIC value in the CS-PVP-I group was still higher than that in the VGD-BZC group although the difference was not significant. The median DII values in the two groups were similar throughout the study period (Table 5).

The median BMIC value in the CS-PVP-I group ($n=40$) was 23.8 $\mu\text{g}/100\text{g}$ and significantly higher than that in the VGD-BZC group ($n=138$) (16.6 $\mu\text{g}/100\text{g}$) during the early neonatal period ($p=0.0236$); however, the mean age when the breast milk samples were obtained was significantly older in the CS-PVP-I group (5.2 ± 1.4 days) than that in the VGD-BZC group (3.6 ± 1.4 days) ($p<0.0001$). At postpartum day 29 there was no difference in the BMIC between the two groups (median: 12.3 *vs.* 14.2 $\mu\text{g}/100\text{g}$).

In the neonatal infants, there was no difference in the median UIC value in the first voiding urine sample between two groups. On day 4, the median UIC in the infants of the CS-PVP-I group was significantly lower than that of the VGD-BZC group. It was still lower without significant statistical differences at one month after birth while the VGD-BZC group contains more breast-fed infants on days 4 and 29 (Table 6).

Discussion

The recommended median UIC for adequate iodine intake is 150–249 µg/L in pregnant women and more than 100 µg/L in lactating women and infants less than 2 years old according to WHO criteria [9]. The overall iodine nutritional status of this population in Yokohama City was adequate in pregnant women (median UIC: 164 µg/L) and lactation women at one postpartum month (median UIC: 107 µg/L). This observation is consistent with our 2005 study in Chiba prefecture [11, 17], where the median UIC values in pregnant and lactating women was 219.0 and 135.0 µg/L, respectively which was higher than those in the present study. However, the median UIC value in lactating women in Study 1 was close to the lower limit of deficiency (101 µg/L) and that in Study 2 was 86 µg/L indicating a decreasing trend of consuming iodine-rich food in this population. Our recent nationwide survey on the iodine nutritional status of Japanese school children revealed adequate iodine intake (median UIC: 269 µg/L) [18]. It is well recognized that even in an iodine-replete area an additional iodine supply might be necessary during pregnancy and lactation despite the iodine sufficiency of schoolchildren [19–21]. Establishment of a monitoring system on dietary habits and urinary iodine concentration in the general population as well as women of childbearing age including pregnant and lactating women are also required in Japan.

Iodine metabolism and thyroid function in mothers during the perinatal period

The median UIC in pregnancy from populations that are both iodine-sufficient or mildly iodine-deficient is generally higher than that in nonpregnant women of reproductive age. We have previously reported that the median UIC increased as early as the eighth week and fluctuated between 194 and 266 µg/L during pregnancy without significant differences, and decreased significantly to 135 µg/L one month after delivery [17]. There are many studies on the changes in UIC or UIE across pregnancy and puerperium, and the results are various; however, the reports on short-time changes in maternal and neonatal UIC during the perinatal period are limited [22–26]. Our longitudinal analysis in the mothers not exposed to iodine showed a significant increase in median UIC on day 2 after birth, then a decrease on day 28, while the median UI/Cr values were not significantly different before and after delivery presumably reflecting the change of urinary Cr excretion due to postpartum renal hyperfiltration.

Some investigators in areas of modest iodine intake are reporting a decrease of UIC after delivery. In Ireland an acute fall of mean UIC (45%) on day 3 after delivery (132 µg/L vs. 76 µg/L) was observed [22, 23]. The same authors reported that the median UIC decreased from 83.5 µg/L to 36 µg/L at delivery (day 0), remained depressed 49 µg/L at day 3 and 63 µg/L at day 10, while that of the non-pregnant control was 91 µg/L [24]. The UIC value at day 5 was approximately 30% lower in Denmark, an area where the median UIE was around 50 µg/L [25]. In Tasmania, Australia where the overall median UIC was 75 µg/L, the median UIC decreased from 69 µg/L to 35 µg/L within 5 days of birth [26]. The discordant results between our studies and others might be related to the iodine status of the studied population. In addition to nutritional iodine status, other factors can interact after delivery to aggravate imbalanced iodine homeostasis. These are increased glomerular filtration rate (GFR)-related iodine losses, accelerated lactation with accumulation of iodine in the mammary gland, or inadequate dietary compensation.

Changes of UIC and iodine balance in neonatal infants during the early neonatal period

In a longitudinal study, we observed that the UIC in the neonatal infants unexposed to iodine increased from 131 µg/L in the first voiding urine sample to 272 µg/L on day 4, then slightly decreased to 265 µg/L on day 28 which were almost identical values to those of Japanese schoolchildren [18]. The estimated UIE ranged from 4.4–48.6 µg/24 h, while the estimated DII by calculating with the amount of milk intake and BMIC was from 0–35.7 µg/24 h in the first 5 days after birth suggesting a negative iodine balance during the early neonatal period. Our UIC and UIE values in infants were much higher than those in previous reports [16, 27–29]. In 16 term Italian infants the mean (SEM) values of UIC were 75.0 (15.6) µg/L in the first urine, 49.0 (10.4) µg/L on day 1, 33.3 (3.3) µg/L on day 5 and 75.5 (12.1) µg/L on days 16–52, while the corresponding values of UIE were 1.7 (0.2) µg/24 h on day 1, 4.1 (0.6) µg/24 h on day 5 and 12.4 (1.7) µg/24 h on days 16–52 [27]. In a 1980s survey in 14 cities of Europe there were marked regional differences of neonatal UIC and the median UIC ranged from 8 to 162 µg/L with the median of 48 µg/L during the neonatal period [28]. A large study on 634 healthy, term Swiss infants revealed that the median UIC on days 0 to 5 was 77 µg/L in the total sample (n=1,212) and there was a gradual increase in median UIC from days 1 through 4. The values were: 58 µg/L at day 0, 68 µg/L at day 1, 75 µg/L at day 2, 82 µg/L at day 3 and 101 µg/L at day 4 after birth. In addition, the authors concluded that the current WHO median UIC cut-off (> 100 µg/L) for iodine sufficiency in infancy may be too high for the first week after birth [16]. Recently, in 334 Turkish mother-infant pairs the median UIC values of maternal UIC, BMIC and infant's UIC on days 4–6 were reported to be 125, 138.0 and 142 µg/L, respectively [29].

The iodine intake of newborn infants is entirely dependent on the iodine content of breast milk and infant formula. A negative iodine balance was observed in healthy term infants at day 28 living in an iodine-sufficient area [30]. In order to achieve a positive iodine balance, the required iodine intake is reported to be at least 15 µg/kg/day in full-term infants [8]. Our results suggested that a substantial amount of iodine has been accumulated in the fetal thyroid gland and thyroidal iodine stores might be not depleted at least by one month after birth in our full-term infant population despite a negative iodine balance during the early neonatal period. However, on day 28 after birth excessive rather than sufficient iodine status was observed in the infants, while maternal UIC levels were indicating iodine deficiency. In lactating mothers with adequate iodine status, an increased fractional iodine excretion into breast milk increases at a lower daily iodine intake, and at the same time a fractional iodine excretion into urine decreases indicating preferential partitioning of iodine into breast milk at lower intakes [31]. Further studies are needed to understand the mechanism of iodine metabolism in both lactating mothers and infants.

Breast milk iodine concentration

Iodine is concentrated into breast milk through increased expression of the sodium iodide symporter (NIS) in lactating breast cells [32]. The iodine concentrations in breast milk are maximal in colostrum, decrease over the next few weeks and remain stable after one month as mature milk in iodine-replete women [33–36]. They are influenced by maternal iodine status and recent iodine intake, duration of

lactation, and maternal fluid intake as well as the sampling procedure of breast milk [37]. Other factors that may influence BMIC are reported to be maternal age, urinary iodine concentration and iodine supplementation, cigarette smoking, salt iodization, and perchlorate [38], an environmental contaminant that acts as a competitive inhibitor of the NIS in the lactating mammary gland [36]. In addition, because breast milk is a complex sample matrix, it has been emphasized that the colorimetric Sandell-Kolthoff method should not be used to measure iodine concentrations in human milk, and ICP-MS is generally recognized as the preferred methodological approach for analyzing total iodine concentrations in human milk [37, 39, 40]. There have been several systematic reviews or meta-analysis on BMIC [33–36, 41]. BMIC varies widely between populations [36], and broad ranges of BMIC have been reported in iodine-sufficient countries [37]. In iodine-sufficient areas higher iodine levels have been reported than in iodine-deficient areas in colostrum (mean: 152.0 vs. 57.8 $\mu\text{g/L}$); however, in mature milk samples the corresponding values did not differ significantly (mean: 71.5 vs. 28.0 $\mu\text{g/L}$) [35]. The largest study on BMIC including 866 lactating women in the long-term iodine sufficient areas of China, the Philippines and Croatia suggested the median and reference range (2.5th and 97.5th percentiles) were 171 $\mu\text{g/kg}$ and 60–465, respectively [31]. In addition, the authors suggested that BMIC was a more accurate biomarker of iodine status in lactating women than maternal UIC as previously proposed [34, 41]. In our study the median (reference range) of BMIC was 176 (111, 355) $\mu\text{g/kg}$ in the early postpartum period and 135 (82, 238) $\mu\text{g/kg}$ at one postpartum month respectively consistent with the results of this large study [37]. In Japan several studies on BMIC values have been reported since 1968 [42–46]; however, except for one report [43] their sample sizes were small and the values were highly variable. BMIC was measured by using Sandell-Kolthoff reaction [43, 45] or ICP-MS [46] or others [42, 44]. The reported mean or median BMIC values were 83 $\mu\text{g/L}$ (n=50) [42], 211.0 $\mu\text{g/L}$ (n=9) [44], 227 $\mu\text{g/L}$ (n=118) [45], 144 (n=22) [46]. These reports cannot be used as a reference for current BMIC in Japanese because of the inappropriate study design including the small number of subjects and methods for BMIC measurement. However, the largest cross-sectional study across almost all divisions of Japan between 1979–1980 showed a decreasing trend of BMIC after delivery and was consistent with previous reports outside Japan. The mean BMIC values were 124.5 $\mu\text{g/L}$ on days 3–5 (n=14), 104.5 $\mu\text{g/L}$ on days 5–10 (n=68), 102.7 $\mu\text{g/L}$ on days 11–20 (n=187) and 66.1 $\mu\text{g/L}$ on days 21–60 (n=735) [43].

Relationship of iodine status and thyroid function between mothers and neonates

In the present study, BMIC positively correlated with maternal UIC or UI/Cr. A positive correlation between BMIC and maternal UIC (UI/Cr) [31, 47–49] or infants' UIC [49–52] has been reported from Denmark [47]. China [31, 48, 49], the Philippines, Croatia [31], Iran and Azerbaijan [51]. We also observed higher BMIC in the women with Cesarean delivery consistent with a previous report in China [52]. In addition, fetal UIC values at birth correlated weakly with maternal UIC values during the perinatal period, but not with neonatal TSH or FT4 during the postpartum month suggesting limited effects of maternal iodine status on neonatal thyroid function in this population.

Effects of PVP-I skin disinfectant on iodine metabolism and thyroid function in mothers and infants

With regard to the effects of skin preparation with aqueous povidone-iodine at a Cesarean operation on iodine metabolism and thyroid function, only a few studies have been conducted on the mothers [53–55], their mature [16, 53, 54, 56–58] or premature infants [59] in the iodine-sufficient areas of Bosnia and Herzegovina [54], Turkey [55], Iran [57, 58], Switzerland [16], UK [59] and China [56], or in Australia, an iodine-deficient area [53].

In iodine-exposed mothers elevated UIC was observed on the second day [54] or at day 4 [53] after a Cesarean delivery; however, in other reports maternal UIC values were not significantly changed 24 hours after delivery [31, 55]. On maternal serum TSH there was only one report indicating that TSH increased with reducing free triiodothyronine in the subjects whose PVP-I was not rinsed off before the Cesarean section [55].

Neonatal UIC values were not significantly changed at 24 hours [55] or at days 0–4 [16] after a Cesarean section, while in another study, a higher neonatal UIC without elevation of TSH was observed in iodine-exposed infants on postnatal day 2 [54]. In a large population study including more than 48,000 mature infants, cord blood TSH and FT4 concentrations and the rates of hyperthyrotropinemia were not affected by the PVP-I used for abdominal preparations in a Cesarean section delivery [57]. Similar results on cord blood TSH and FT4 values have been reported [56, 58]; however, a significant higher incidence of elevated TSH with reduced T4 concentrations was reported in the iodine-exposed infants [58].

Neonatal TSH and FT4 values in the iodine-exposed infants were not significantly different from those in the control group at 12, 48 and 120–h after a Cesarean section in which the PVP-I antiseptic was rinsed off with 70% alcohol solution [56]. In addition, despite elevated maternal UIC, there was no significant difference in neonatal TSH values on postnatal days 3–5 between the two groups [53, 54]. On the contrary, a higher blood TSH value at 72–96 h without elevated UIC was observed in iodine-exposed infants [16]. It is also reported that serum TSH and FT4 concentration in the iodine-exposed preterm infants (< 32 weeks' gestation) were higher than those in the unexposed infants on postnatal days 7, 14 and 28 [59].

In the present study, after short-time exposure to 100 mL of 10% PVP-I solution, increased serum iodine concentration and markedly elevated urinary iodine excretion were observed in the mothers of the CS-PVP-I group between postpartum days 2 and 3; however, the serum TSH concentration decreased slightly. In the neonatal infants there were no significant differences in blood TSH and FT4 values between the two groups, and the UIC of the infants in the CS-PVP-I group was not higher than that of the infants in the VGD–BZC group at birth and on postnatal days 4 and 29. One possible reason for the higher UIC observed in the infants of the VGD–BZC group might be due to the higher prevalence of breast feeding in this group. Actually, the median UIC value in the infants nursed mainly with breast milk was significantly higher than that of the other infants.

Our results clearly showed that even if PVP-I was washed off within several minutes after its application, the iodine in PVP-I was absorbed into the blood stream and excreted in the urine, but did not affect BMIC, maternal FT4, neonatal UIC, TSH, or FT4 during the perinatal period consistent largely with previous

reports [16, 54–59]. Possible reasons why the iodine disinfectant had little effect on maternal and fetal thyroid function in our study are that the amount of iodine left on the maternal skin after washing off the PVP-I solution may be too small to affect thyroid function, and/or the time between application of iodine to the mother and ligation of the umbilical cord of the fetus was too short to allow the absorbed iodine to pass through the placenta to the fetus.

Although the amount of PVP-I absorbed through intact skin is uncertain, the amount of permeated iodine might depend on the concentration of PVP-I and the size of the area which it is applied. According to the percutaneous iodine absorption experiments using a human abdominal skin specimen (4×4 cm²), 1.9 ± 1.0% of iodine in 10% PVP-I solution containing 0.606 g/cm² of iodine was absorbed through the skin in a time-dependent manner after 24 h [60]. Significant transcutaneous iodine absorption might occur in the large areas cleaned before a Cesarean operation although the skin of healthy adults is less permeable than that of neonates or preterm infants. The association between the dose of iodine administered and thyroid function is controversial. Further studies are necessary to define the critical value of urinary iodine concentrations in full-term neonates in an iodine-sufficient area that may lead to the impairment of thyroid function.

There are limitations in the present study which include a relatively smaller sample size, different study locations and study periods that may lead to bias in sample selection. The strengths are a longitudinal prospective study which may be expected to minimize the inter-individual variation, the use of ICP-MS to measure BMIC, and the assessment of maternal-neonatal iodine metabolism by measuring BMIC, UIC, serum iodine, TSH, and FT4 during the perinatal period. The UIC in the neonatal infants was determined including the first voiding urine sample which represents the iodine status of a fetus in utero. In most studies on the effects of PVP-I on maternal and neonatal thyroid function and iodine metabolism, the amount of PVP-I used or the time of contact with the skin are not mentioned in detail, but we have strictly defined them.

Conclusions

Our results provide additional information on iodine metabolism and thyroid function as well as the effects of PVP-I during the perinatal period in lactating mothers and their neonatal infants residing in an iodine-replete area. Maternal and neonatal iodine excretion was higher in this population than that in an iodine-deficient area suggesting adequate iodine intake in this population as well as sufficient iodine reserve in neonatal thyroid at birth. However, at one postnatal month the UIC in lactating mothers was low enough to iodine deficiency or near iodine deficiency. Further studies on the iodine status in lactating mothers are necessary in Japan. PVP-I antiseptics at a Cesarean delivery transiently increased the iodine concentration of maternal serum, urine and breast milk, while it had little effect on maternal and neonatal thyroid functions as long as the doses and usage of PVP-I were the same as those used in this study.

Declarations

Author Contribution

All the authors contributed to the study conception and design. The authors' responsibilities were as follows—Y.F., Y.I., Y.S. and M.I. designed the research; Y.F., H.O., M.T. and Y.F. conducted the research; and Y.F. analyzed and interpreted the data and wrote the first draft of the manuscript. All the authors read and approved the final manuscript. Y.F. was the principal investigator and had primary responsibility for the final content.

Data Availability

The data that support the findings of this study are not available.

Ethics approval and Consent

This study was conducted in accordance with the ethical guidelines contained in the Declaration of Helsinki and Medical Research Involving Human Subjects including epidemiological research, and written informed consent was obtained from each participant included in the study at the initial study visit. The study protocol was reviewed and approved by the joint Ethics Committee of Ogawa Clinic and Nakamachidai Ladies Clinic, Yokohama, Japan on May 2010.

Conflict of interest

The authors declare no competing interests.

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Tables

Table 1-6 is available in the Supplemental Files section.

Figures

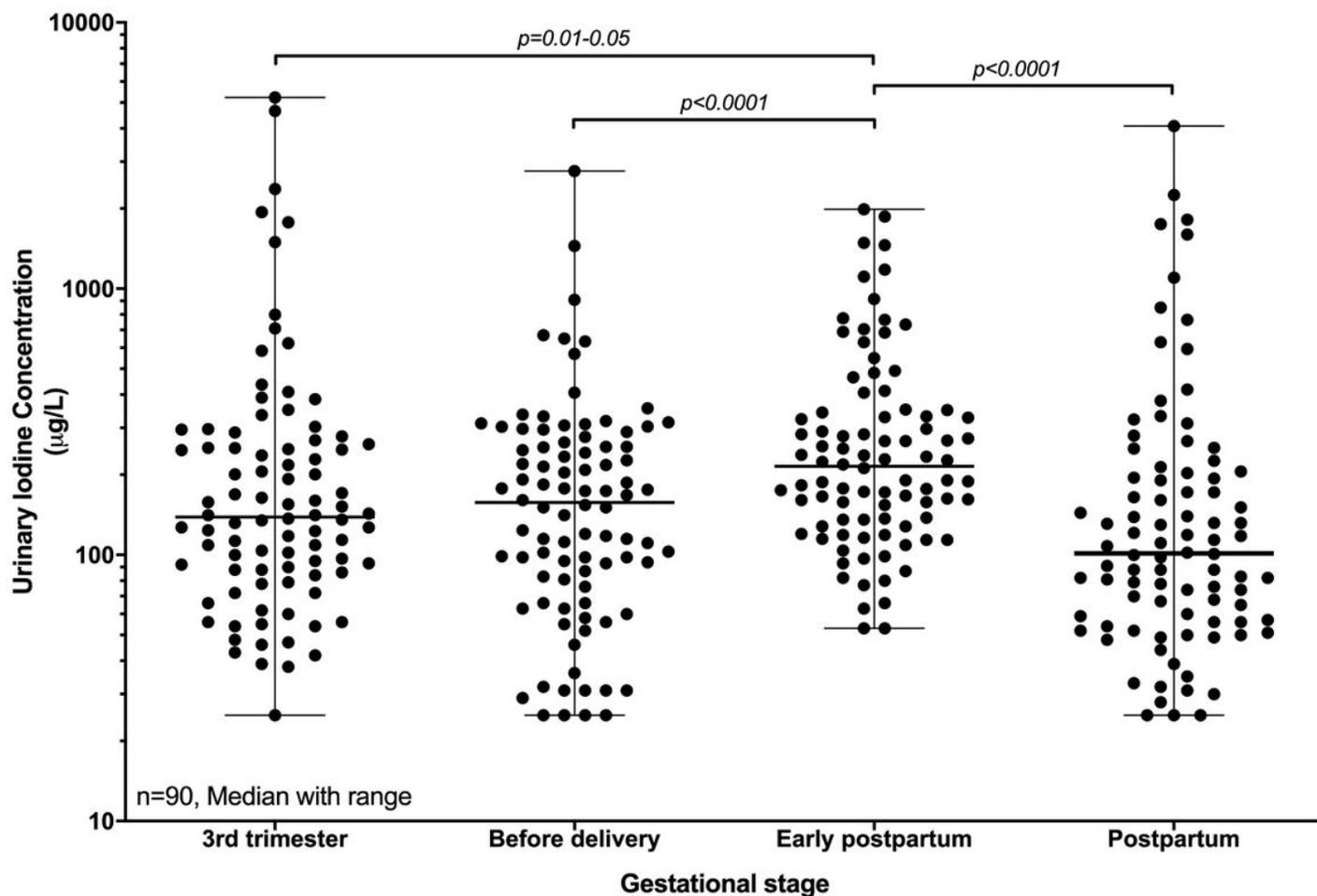


Figure 1

Perinatal change of urinary iodine concentration in the pregnant women not exposed to iodine-containing disinfectants in Study 1 (Repeated measurement)

n=90, Median with range. Urine samples were collected at the following times: 3rd trimester: 32.5±1.1 gestational weeks, Before delivery: 10.6±10.8 h, Early puerperium: 44.4±6.0 h, Late puerperium: 29.5±2.0 days

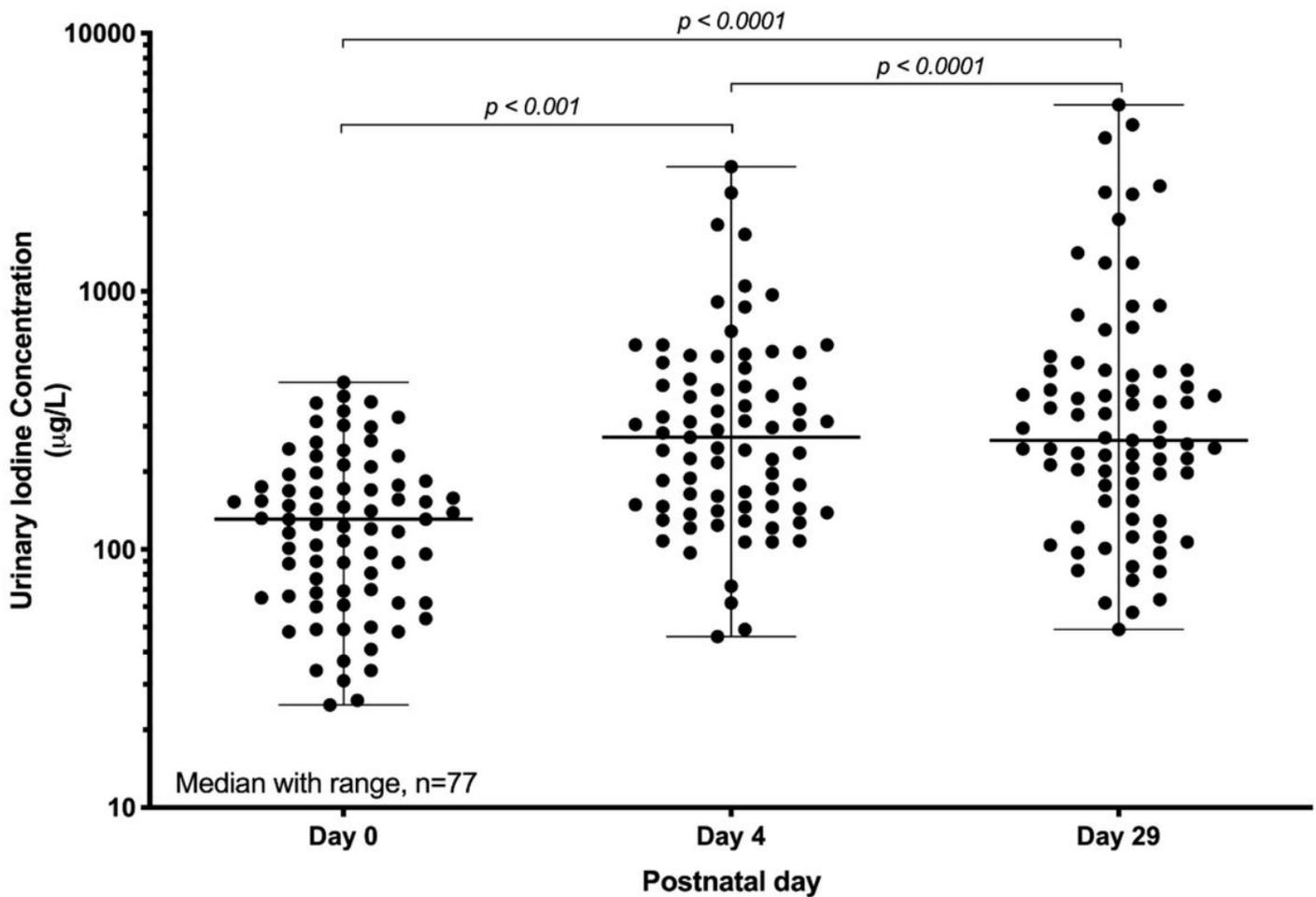


Figure 2

Postnatal change of urinary iodine concentration in the infants born to the mothers not exposed to iodine-containing disinfectants in Study 1 (Repeated measurement)

n=77 (43 males and 34 females), Median with range. Urine samples were collected at the following times: Day 0: at birth in the first voiding urine, Day 4: 4.9 ± 0.5 days, Day 29: 28.9 ± 2.0 days (Mean \pm SD).

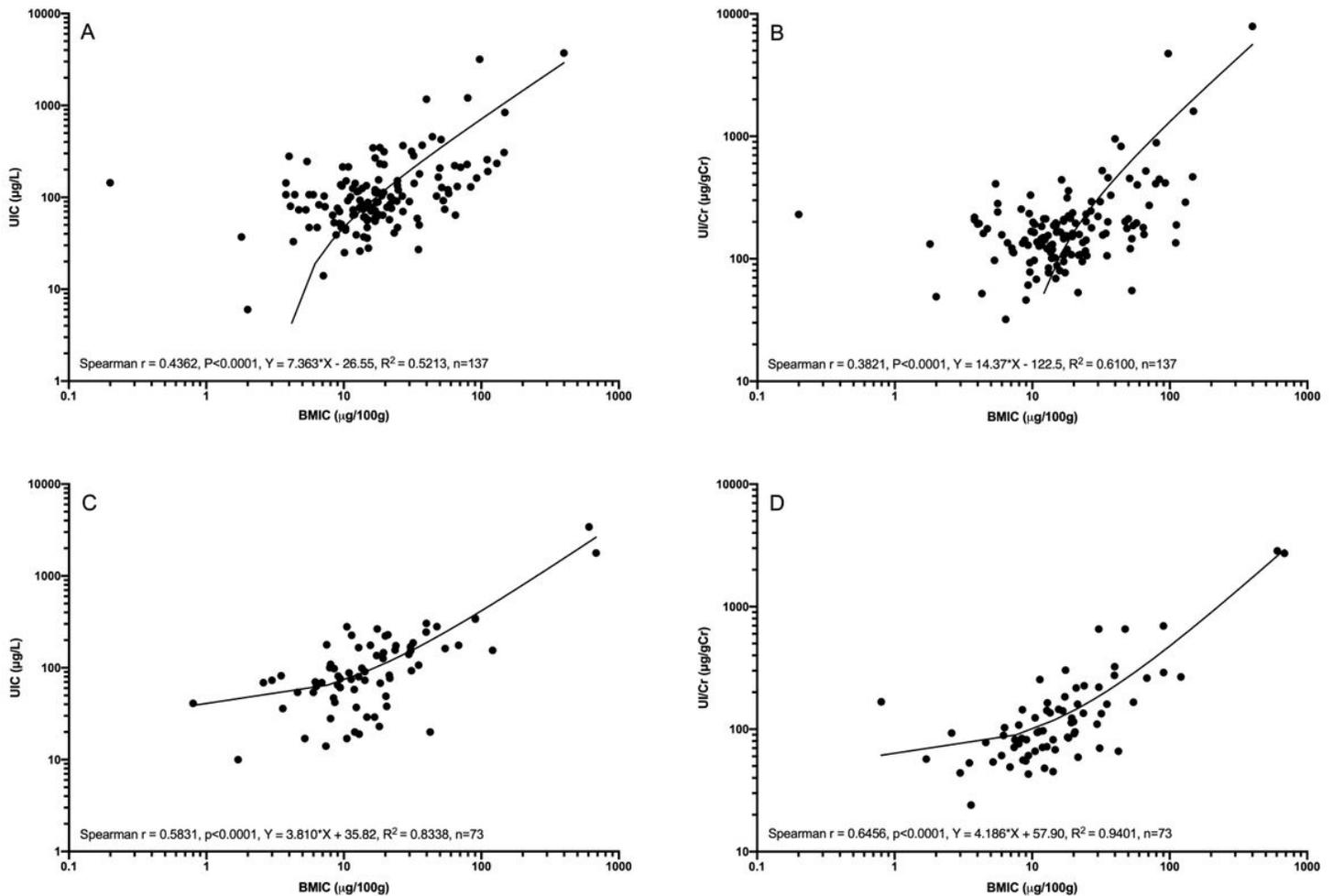


Figure 3

Correlation between maternal UIC or UI/CR and BMIC in the lactating women not exposed to iodine-containing disinfectants (PVP-I)

Scatter plots of samples from the lactating women not exposed to iodine-containing disinfectants (PVP-I) illustrating the correlation between (A) maternal UIC at the 4th day of puerperium and BMIC, (B) maternal UI/CR at the 4th day of puerperium and BMIC, (C) maternal UIC on the 33th day of puerperium and BMIC, and (D) maternal UI/CR on the 33th day of puerperium and BMIC. BMIC: breast milk iodine concentration, UIC: urinary iodine concentration, UI/CR: urinary iodine concentration relative to creatinine, PVP-I: povidone-iodine.

Supplementary Files

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