Original Article

Urine Iodine Level in Iodine-Supplemented Pregnant Women: Oral Tablet versus Iodized Oil

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Background: Although the policy of universal salt iodization and daily iodine-containing vitamin supplementations were implemented, the urinary iodine concentration (UIC) in pregnant women in the northeast of Thailand still showed mild iodine deficiency.

Objective: To determine UIC in pregnant women receiving daily iodine-containing vitamin versus a single dose of two iodized oil capsules.

Materials and Methods: The present study was conducted between March 2014 and October 2015, in 21 public hospitals in Khon Kaen Province. Healthy singleton pregnancy of a gestational age of less than 20 weeks that had not received iodine-containing vitamin were enrolled. The participants were asked to take either daily one tablet vitamin or a single dose of two iodized oil capsules. Random urine was collected before and after taking medication. Neonatal thyroid stimulating hormone (TSH) was retrieved from medical record.

Results: Of the 2,079 participants, median UIC of pre- and post-daily vitamin supplementation in 1,061 pregnant women were 116.0 and 126.2 mcg/L. Median UIC of pre- and post-single dose iodized oil in 973 participants were 110.4 and 108.6 mcg/L. There was no statistically significant increase UIC post iodine supplementation in both groups (p=0.169). The median neonatal serum TSH were 4.34 and 3.79 mU/L in daily vitamin and single dose respectively, which is significantly lower in the iodized oil group (p=0.023).

Conclusion: Post iodine supplementation either by daily vitamin or single dose did not significantly increase UIC.

Keywords: Iodine supplementation, Iodized oil, Urinary iodine concentration

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Iodine is an essential trace element for human. It is the substrate for thyroid hormone production[1]. Thyroid hormone plays major roles in regulating body metabolism and neurodevelopment in fetus. Severe hypothyroidism during pregnancy can cause fetal brain damage and mental retardation[2,3]. Mild to moderate iodine deficiency cause a wide range of disorders in all age group including cognitive impairment in children, low IQ, delayed physical development, menstrual disorder, and impaired mental function[3-5]. Universal salt iodization (USI) program is suggested to eliminate iodine deficiency disorder in community[6]. Urinary iodine concentration (UIC) can reflect adequacy of iodine intake (150 to 249 mcg/L)[6]. In addition, median neonatal blood thyroid stimulating hormone (TSH) higher than 5 mIU/L, equivalent to serum TSH 11.2 mIU/L, less than 3% in community can reflect adequate iodine intake area as well[6]. Although the policy of USI has been implemented for many years, the median UIC in pregnant women was 113.3 mcg/L in year 2013 in Khon Kaen province[7]. In addition, the IQ in school-age children in the northeast region was the lowest compared with other regions in Thailand[8]. In area that median UIC in pregnant women is less than 100 mcg/L and household use less than 90% iodized salt, the World Health Organization (WHO) suggests using concentrate iodine via orally or intramuscular injection[9,10]. Iodized oil is concentrated iodine that can prolong release iodine after intramuscular

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injection or taken orally for 6 to 12 months[9,10]. It is cheap, convenient to use, and has few side effects[11-15].

Aside from conventional prescribing daily iodine-containing prenatal vitamin, which contain iodine 150 to 200 µg/tablet, an annual single dose of two iodized oil capsules is the alternative choice for pregnant women in four provinces, notably Khon Kaen, Roi Et, Mahasarakham, and Kalasin, in the northeast region of Thailand in last two years.

The authors hypothesized that patient's compliance might be the main factor to cause inadequate iodine intake. Therefore, an annual dose of iodine can overcome this problem. The present study aims to determine UIC in pregnant women that received daily iodine-containing vitamin or a single dose of two iodized oil capsules.

Materials and Methods

The study was approved by the Khon Kaen University Ethics Committee for Human Research (HE 561352). A prospective cohort study was conducted at three provincial and 18 district public hospitals in Khon Kaen Province between March 2014 and October 2015. The sample was selected proportional to birth rate per year in each hospital. The authors included singleton pregnancy, gestational age less than 20 weeks, and had not received iodine-containing prenatal vitamin. Exclusion criteria were pregnant women who had underlying diseases including pregnancy induced hypertension, hyper- or hypothyroidism, kidney disease, heart rate higher than 120 beat per minute, and allergic to iodine substance. Informed consents were obtained from all participants. The pregnant women were asked to take either daily tablet of iodine-containing prenatal vitamin (Obimin AZ®: Great Eastern Company), containing iodate 200 µg/tablet or (Triferdine®: GPO, Thailand), containing iodide 150 µg/tablet, depending on each hospital, or a single dose of two iodized oil capsules (Lipiodol®: Guerbet Company, Paris, France) containing iodine 200 mg/capsule, with daily tablet of iron without any additional iodine-containing medication throughout pregnancy. The first 30 mL of urine sample was collected before receiving the medication. Then the patient had to swallow the medication before going back home. The second 30 mL sample of urine was random and was collected at gestational age 32 to 36 weeks. In case of loss to follow-up, two to three telephone calls were made to contact the participants. All urine specimens were transported from each hospital to the main center and kept in 4 degree Celsius until analyses. Urinary iodine determination was performed using a simple microphate method described by Ohashi et al[16]. Ammonium persulfate, arsenic trioxide, sulfuric acid, sodium chloride, ceric ammonium sulfate, and potassium iodate were used for analysis (Sandell-Kolthoff reaction). The calorimetric measurements were performed by TECAN automatic analyzer (Roche, USA). Laboratory center had been qualified by the Laboratory Center of Bureau of Nutrition, which jointly collaborated with Ensuring the Quality of Urine Iodine Procedure (EQUIP) of Center of Disease Control and Prevention (CDC), USA since 2001.

Currently, neonatal TSH was routinely studied due to the national neonatal hypothyroidism screening policy. The cutoff point of abnormal high was more than 11.2 mIU/L, referred to laboratory reference of the Department of Science, Ministry of Public Health. The authors retrieved the data from each hospital where the baby was born.

A sample sizes of 1,105 in each group produced a two-sided 95% confidence interval (CI) for the difference in population proportions with a width that was equal to 0.080 when the estimated sample proportion 1 was 0.70, the estimated sample proportion 2 was 0.50, and the difference in sample proportions was 0.20[17].

Statistical analysis

Statistical analyses were performed using Stata, version 10 (StataCorp LP, College Station, TX, USA). Mean ± standard deviation (SD), median (P25, P75) were used for continuous data. The number and percentage were used for categorical data. Spearman's correlation was used for non-normal distribution data. Statistical significance was defined at p-value less than 0.05.

Results

Two thousand seventy-nine pregnant women participated in the present study. One thousand eighty-one pregnant women decided to take daily iodine-containing prenatal vitamin throughout pregnancy, and 998 women preferred to have a single dose of two capsules of iodized oil orally. Pre-iodine supplementation UIC was measured in 1,061 and 973 urine samples in prenatal vitamin group and iodized oil group, respectively. Eight hundred sixteen and 684 pregnant women were available for UIC post iodine supplementation at 32 to 36 weeks in prenatal vitamin and iodized oil capsule groups. There was 1.4% (27 in 1,904) and 1.7% (28 in 1,701) of urine samples in

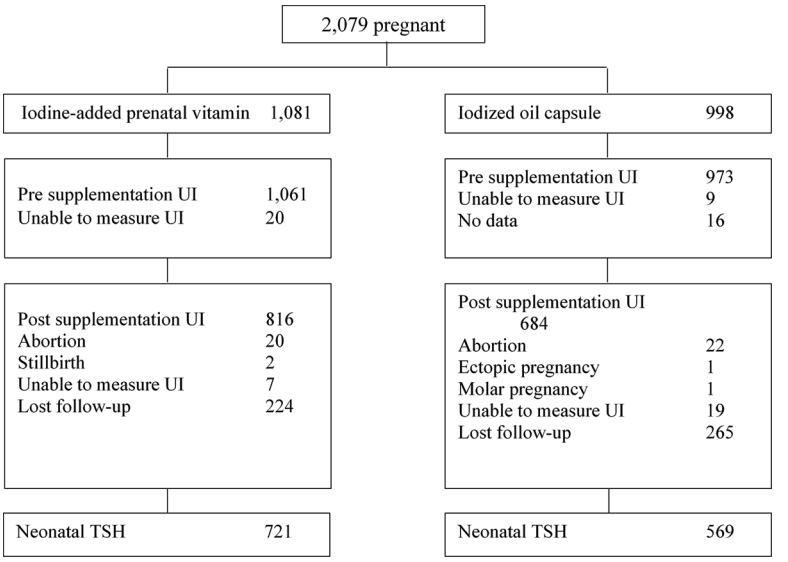

Figure 1. Flow of participants.

Table 1. Baseline characteristics of participants (n=2,079)

	Iodine-containing prenatal vitamin (n=1,081); n (%)	Iodized oil capsule (n=998); n (%)
Age (year); mean±SD	25.4±6.7	25.3±6.4
Parity		
Nullipara	476 (44.0)	436 (43.7)
Multipara	605 (56.0)	562 (56.3)
Education		
Primary school	113 (10.4)	119 (11.9)
Secondary school	546 (50.5)	529 (53.0)
Vocational school	206 (19.1)	199 (19.9)
Bachelor degree and higher	217 (20,1)	151 (15.1)
Income per month (Thai Baht)		
<10,000	373 (34.5)	347 (34.8)
10,000 to 15,000	368 (34.0)	334 (33.5)
>15,000	340 (31.4)	317 (31.8)
Pre-pregnancy BMI (kg/m^2); mean±SD	21.8±4.2	21.7±4.3
GA at first ANC (weak); mean±SD	11.1±3.9	11.0±3.8
GA at delivery (weak); mean±SD	37.6±4.5	37.7±4.5
Birth weight (g); mean±SD	3,077.6±434.7	3,054.1±440.9
Complication during pregnancy		
No	492 (78.2)	492 (78.5)
Yes	137 (21.8)	135 (21.5)
Complications during labor and postpartum		
No	547 (87.7)	558 (87.3)
Yes	77 (12.3)	81 (12.7)
Side effects of drug		
No	652 (99.4)	622 (100)
Yes	4 (0.6)	0 (0.0)
Fetal abnormality		
No	647 (98.9)	623 (99.5)
Yes	7 (1.1)	3 (0.5)

BMI=body mass index; GA=gestational age; ANC=antenatal care; SD=standard deviation

Table 2. Comparing urinary iodine concentration between daily vitamin and iodized oil capsule

Urinary iodine concentration (ug/L)	Iodine-containing prenatal vitamin (n=1,061); n (%)		Iodized oil capsule (n=973); n (%)		Difference (95% CI)	p-value
	Pre (n=1,061)	Post (n=809)	Pre (n=973)	Post (n=665)		
Median (P25, P75)	116.0 (66.3, 180.8)	126.2 (73.0, 217.6)	110.4 (64.6, 72.0)	108.6 (62.9, 181.1)	8.83 (–3.76 to 21.42)	0.169
<20	36 (3.4)	15 (1.9)	28 (2.9)	17 (2.6)		
20 to 50	136 (12.8)	93 (11.5)	143 (14.7)	106 (15.9)		
51 to 99	289 (27.2)	207 (25.7)	276 (28.4)	187 (28.2)		
100 to 149	227 (21.4)	157 (19.5)	222 (22.8)	128 (19.3)		
150 to 249	249 (23.5)	180 (22.3)	205 (21.1)	156 (23.5)		
250 to 499	113 (10.7)	144 (17.6)	85 (8.7)	69 (10.4)		
>500	11 (1.0)	13 (1.6)	14 (1.4)	02 (0.4)		

CI=confidence interval

Table 3. Neonatal TSH in iodine-supplemented mothers (n=1,290)

TSH (mU/L)	Iodine-containing prenatal vitamin (n=721); n (%)	Iodized oil capsule (n=569); n (%)	Difference; 95% CI	p-value
Median (P25, P75)	4.34 (2.87, 6.5)	3.79 (2.46, 6.27)	0.05 to 0.60	0.023
TSH >11.2 mU/L	40 (5.55)	30 (5.27)	–2.21 to 2.75	0.828
TSH >25 mU/L	2 (0.28)	0 (0.00)	–0.11 to 0.66	0.209

TSH=thyroid stimulating hormone; CI=confidence interval

Table 4. Correlation between urinary iodine concentration and neonatal TSH

	R	p-value	95% CI
Post supplementation			
Iodine-containing prenatal vitamin	–0.109	0.147	–0.252 to 0.039
Iodized oil capsule	0.003	0.969	–0.141 to 0.146

CI=confidence interval

both groups that could not be measured for UIC due to contamination. Two hundred twenty-four from 1,081 (20.7%) and 265 from 998 (26.6%) pregnant women in the prenatal vitamin group and the iodized oil group were lost to follow-up and missed the second urine collection. Data of 721 and 569 neonatal serum TSH were available (Figure 1). Baseline characteristics of participants were similar in two groups as shown in Table 1.

Pre iodine supplementation median UIC were 116.0 (66.3, 180.8) and 110.4 (64.6, 172.0) mcg/L in the prenatal vitamin and the iodized oil group, respectively. Post iodine supplementation median UIC were 126.2 (73.0, 217.6) and 108.6 (62, 181.1) mcg/L in prenatal vitamin and iodized oil groups, respectively. There was no statistical increase of UIC post iodine supplementation in both groups (95% CI –3.76 to 21.42, p=0.169) (Table 2).

Median neonatal serum TSH were 4.34 (2.87, 6.5) and 3.79 (2.46, 6.27) mU/L in vitamin and iodized oil group, which was statistically significant lower TSH in iodized oil group (95% CI 0.05 to 0.60, p=0.023) (Table 3). However, there was no statistically significant difference of TSH higher than 11.2 mU/L cases in both groups. Five-point-fifty-five percent and 5.27% of neonate in each group had TSH higher than 11.2 mU/L. However, only 0.28% (2 in 721) baby in the prenatal vitamin group had TSH more than 25 mU/L and needed further thyroid function evaluation. There was no correlation between maternal UIC and neonatal TSH in both groups (r=–0.109, p=0.147 and r=0.003, p=0.969) (Table 4).

Discussion

Median UIC of pre iodine-supplemented pregnant women in Khon Kaen province was less than 150 mcg/L in both daily vitamin and iodized oil group, which classified as mild iodine deficiency according to WHO criteria)[6]. There was a slight increase of median UIC in pre iodine supplementation when compared with previous studies in Thailand[18,19] and other developed countries[20]. In contrast to Sukkhaojaiwaratkul et al's study[21], which was conducted in 1,508 pregnant women at Ramathibodi Hospital in Bangkok, the capital city of Thailand between 2011 and 2013, it found that median UIC

of pre iodine supplementation was 170.6 (7.7 to 1,499.3) mcg/L, which represented an adequate iodine intake. The possible reason was the present study composed of pregnant women in rural northeastern area, which is different in socioeconomic, educations, and occupations.

Median UIC in post daily 150 to 200 mcg of iodine-containing prenatal vitamin group had slightly increased in median UIC but did not occurred in iodized oil supplementation group. Post supplementation still showed mild iodine deficiency in both groups. This is in contrast to the study in Bangkok[21] that showed an increasing of median UIC after prescribed 150 mcg of iodine in daily prenatal vitamin tablet.

The authors reported the iodine deficiency pregnant population that failed to increase UIC after oral iodine supplement. Neither iodine-containing prenatal vitamin nor iodized oil capsule could increase urinary iodine. The present study finding was consistent with failure of increasing urine iodine in northeastern provinces of Thailand after USI policy?[7]. The authors postulate that there may be problem of iodine absorption, together with iodine deficiency in northeastern provinces of Thailand. According to sodium iodide symporter (NIS), an intrinsic membrane protein, mediates the transport of iodide into the thyroid. NIS is present in enterocytes of the small intestine[22]. NIS may play important role in absorption of iodine from small bowel. Much mutation in NIS gene caused iodine-transport disease that present with goiter or hypothyroidism. However, epidemiological study in Chinese congenital hypothyroidism population found a very small number of NIS gene mutations. That mean gene mutations may not be the explanation for large population of iodine deficiency[23]. Post-translation regulations of NIS may be the better explanation for the present finding. NIS in enterocytes is regulated at least by iodine[22]. It was possible that some genetic or environment factors may decrease expression of NIS and iodine absorption. Recently, Na+/multivitamin transporter (SMVT) was demonstrated to be an alternative iodine absorption in enterocytes. SMVT is a transporter of anion vitamin such as biotin, a-lipoic acid, and pantothenic acid. Iodine may compete with many vitamins for an absorption. Thiocyanate, obesity, diarrhea, iron deficiency anemia, selenium deficiency, and parasitic infestation are the possible causes of interfere drug efficacy, but the present study have no data about those possible causes[24,25]. Poor compliance may be another possible explanation in daily taken prenatal vitamin. However, failure of increasing urine iodine in iodinated oil is least likely.

Maternal UIC in both groups were not significantly increased post iodine supplementation. This contrasted to the other studies in Thailand[21,26]. The neonatal TSH was significant lower in the iodized group. However, number of median TSH higher than 11.2 mU/L cases were not statistically different and occurred in more than 3% in both groups, which indicated mild iodine deficiency area according to WHO criteria[6].

The present study major limitation was high rate of missing of the second urine collection. The possible causes were changing place for antenatal care and delivery and change of telephone number.

The present study enrolled large sample size and most of participants were in suburb area with low to moderate socioeconomic status, which represented the real community. However, high rate of loss follow-up of the second urine sample at third trimester was the major limitation. In addition, the authors did not assess the medication adherence in the daily intake prenatal vitamin group.

Result of the present study will lead to the next study to verify the present study results and identity the causes of poor iodine absorption in this population, while the campaign of USI should be continued.

Conclusion

Post iodine-supplemented pregnant women in Khon Kaen province either by daily iodine-containing prenatal vitamin group or iodized oil group failed to increase UIC dramatically. However, there was statistically significant lower neonatal TSH in iodized oil supplementation group.

What is already known on this topic?

The previous study of Sukkhaojaiwaratkul et al[20] in 2014 showed significant increase UIC post supplementation daily tablet of iodine-containing prenatal vitamin.

What this study adds?

This study provided contrary results that failed to increase UIC after oral iodine supplementation. However, there was a statistically significant lower neonatal TSH in iodized oil supplementation group.

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Conflicts of interest

The authors declare no conflict of interest.

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