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Original Article

Maternal iodine insufficiency and adverse pregnancy outcomes

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Abstract

This study aimed to assess the iodine status of pregnant women in each trimester and to compare the pregnancy outcomes between groups with iodine insufficiency and iodine sufficiency. Longitudinal study on urinary iodine concentration (UIC) in each trimester as well as comparison between women with iodine insufficiency (<150 mcg L^{-1}) and iodine sufficiency was conducted. Pregnant women without thyroid diseases who had not received iodine supplementation were recruited for UIC measurements in each trimester and were followed up for pregnancy outcomes. In the analysis of 384, 325 and 221 samples in the first, second and third trimester, the medians of UICs were 147.39, 157.01 and 153.07 mcg L^{-1}, respectively. Of 399 women, 174 (43.6%) had a UIC less than 150 mcg L^{-1} (suggesting iodine insufficiency) and 225 (56.4%) had a UIC greater than or equal to 150 mcg L^{-1} (suggesting iodine sufficiency). Of 390 women with availability of the final outcomes, 171 and 219 in the insufficiency and sufficiency group, respectively, the rates of preterm birth and low birthweight were significantly higher in the insufficiency group, 17.5% vs. 10.0% ($P = 0.031$) and 19.9% vs. 12.3% ($P = 0.042$), respectively. Logistic regression analysis showed that iodine status was an independent risk of preterm birth and low birthweight. Finally, women with a UIC <100 mcg L^{-1} had a significantly higher rate of fetal growth restriction, 13/68 vs. 30/322 ($P = 0.031$). In northern Thailand, a great number of pregnant women had a median UIC less than 150 mcg L^{-1} and they had a higher risk of preterm birth and low birthweight. Finally, those with a median UIC of less than 100 mcg L^{-1} had a higher risk of fetal growth restriction.

Keywords: iodine, pregnancy, outcomes.

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Introduction

Iodine deficiency has been a significant health problem worldwide and affects both industrialized and developing countries. The ongoing monitoring of iodine status in the population remains essential, and special attention needs to be paid to monitor the status of vulnerable population, such as pregnant women and infants. Recent data on urinary iodine excretion in adults as well as newborns indicate a high prevalence of iodine insufficiency in many countries (Hetzel 1983; Zimmermann & Andersson 2012; Pearce 2013). These cases may manifest as subclinical hypothyroidism in neonates, or as goitre in adolescents and adults. Iodine insufficiency causes not only goitre but also mental deficiency, hearing loss and other neurological impairments, as well as short stature secondary to thyroid insufficiency. Although iodinated salt should be available in most countries where it is needed, its quality and share of the market are often unsatisfactory. Dietary iodine requirement is increased during pregnancy due to increased

thyroid hormone production, increased renal iodine loss and fetal iodine requirements. Adequate amount of iodine is essential for fetal neurological development immediately after conception, and such abnormalities are dependent on the degree of insufficiency. The degree of insufficiency varied from countries to countries. Therefore, each geographical area should have its own baseline data of the status of iodine intake. The World Health Organization (WHO) has estimated that at least 50 million people worldwide have varying degrees of preventable brain damage due to iodine deficiency (WHO, UNICEF, ICCIDD 2007). Although it is doubtful whether mild insufficiency causes intellectual impairment or not, iodine supplementation does prevent fetal goitre (Stagnaro-Green *et al*. 2012). Severe insufficiency, on the other hand, is frequently associated with damage typically encountered with endemic cretinism (Delange 2001). It is presumed that moderate insufficiency has intermediate and variable effects.

Although several reports have documented the effects of iodine insufficiency on fetal neurodevelopment and some authors have observed a potential risk of fetal growth restriction (FGR) or low birthweight (LBW) among pregnancies with iodine insufficiency (Boyages 1993; Zimmermann 2009), little has been known about the effects of iodine insufficiency on pregnancy outcomes such as preterm birth (PTB), growth restriction or pre-eclampsia. Furthermore, very few studies have assessed iodine status in each trimester of pregnancy. In our practice, we have not routinely supplemented iodine to pregnant women, although some hospitals and clinics have. Only iron supplementation has been routinely prescribed to pregnant women, and folic acid supplementation is optional. Currently, national policy has been developed to support routine iodine supplementation. However, before implementation, we need to determine the baseline iodine status in our obstetric population. Therefore, we conducted this study to assess the iodine status of pregnant women in each trimester and to compare the pregnancy outcomes between women with iodine insufficiency and iodine sufficiency.

Subjects and methods

This study, including longitudinal measurements of urinary iodine concentrations (UICs) throughout pregnancy and comparison of pregnancy outcomes between women with iodine insufficiency and iodine sufficiency, was carried out at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Thailand, with ethical approval granted by the institutional review boards. Pregnant women who are attending our antenatal care clinic during 1 September 2013 and 31 October 2014 were invited to participate in the study with written informed consent. The inclusion criteria were (1) singleton pregnancy; (2) Thai ethnicity; (3) reliable gestational age based on certain and regular menstrual period consistent with clinical estimation on early gestation or fetal sonographic biometry in the first half of pregnancy; and (4) no thyroid diseases. To avoid heterogeneity of study population, only Thai ethnic women were included. Exclusion criteria consisted of (1) multifetal pregnancies; (2) previously or currently diagnosed for any thyroid diseases or history of thyroid treatment; (3) receiving iodine-containing supplements; and (4) loss to follow-up or unavailability of the pregnancy outcomes.

The main outcome measures were (1) median of UICs in each trimester and patterns of UIC changes among the three trimesters; (2) iodine status among our obstetric population, categorized as insufficiency, adequacy, above requirement and excessive levels, as

Key messages

- Iodine insufficiency is prevalent in many regions of the world. Pregnant women in the northern part of Thailand have a median urinary iodine concentration (UIC) less than 150 mcg L^{-1}.
- A maternal UIC less than 150 mcg L^{-1} significantly increases the risk of preterm birth and low birthweight.
- A maternal UIC less than 100 mcg L^{-1} significantly increases the risk of fetal growth restriction.
- In this population, the median UIC is relatively constant over the three trimesters of normal pregnancy.

well as the proportion of women with iodine insufficiency among non-supplemented pregnant women. The criteria of insufficiency, adequate, above requirement and excessive in this study, were defined as a median UIC of less than 150, 150–249 and 250–449 $\mu g\ L^{-1}$, and more than 500 $\mu g\ L^{-1}$, respectively, based on the international WHO, UNICEF, ICCIDD (2007) criteria; and (3) a comparison of pregnancy outcomes between women with iodine insufficiency and iodine sufficiency, including rates of FGR, PTB, LBW, pre-eclampsia or pregnancy-induced hypertension (PIH), antepartum haemorrhage (placenta previa and placental abruption), low Apgar scores at 1 and 5 min, and caesarean section. The maternal baseline characteristics and obstetric outcomes were also evaluated. The following variables were assessed: parity, number of antenatal visits, gestational age at delivery, route of delivery, pregnancy outcomes including abortion (defined as ending up before 24 weeks), PTB (delivery before 259 days of gestation), LBW (birthweight of less than 2500 g), FGR (birthweight of less than 10th percentile for gestation age), gestational diabetes, pre-eclampsia or PIH, postpartum haemorrhage, low Apgar scores (less than 7) at 1 and 5 min, and stillbirth.

A 30-mL sample of early morning urine was collected from each women using a screw-capped plastic bottle and then frozen at –70°C in the laboratory until analysis. Samples were analysed in batches of 20 samples at a time. The analysis was carried out using inductively coupled mass spectrometry (WHO, UNICEF, ICCIDD 2007). External quality control monitoring was performed by regular participation in Ensuring the Quality of Urinary Iodine Procedures, Centers of Disease Control and Prevention, United States of America.

Women recruited in the study were treated in routine standard antenatal care. The results of iodine status were not disclosed until the end of the study and were not used for any clinical decisions.

Statistical analysis

All statistical analyses were performed using SPSS version 21.0 (released 2012; IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). The baseline characteristics of the pregnant women were compared using Student's *t*-test for quantitative data and chi-square for categorical variables. UICs in each trimester were compared using analysis of variance (repeated measures) test using linear mixed models: UIC as a dependent variable and trimester as a factor or repeated variable that was also used in fixed effect model. The associations of iodine status and adverse pregnancy outcomes were analysed using Pearson's chi-square test. Multivariate binary logistic regression was performed to control the potential confounders such as age, parity, body mass index and the number of antenatal care visits, on unweighted data, to assess the amount to which iodine status might affect the odds of main pregnancy outcomes identified. In comparison with the gestational age at delivery between group with iodine sufficiency and insufficiency, given a mean difference of 1 week with standard deviation (SD) of 3 weeks, at 95% confidence interval (CI) and 80% power of test, the study needed at least 142 women per group. A P-value of <0.05 was considered statistically significant.

Results

Of all 410 women recruited, 11 were excluded because of unavailability of the final outcomes (four cases) and receiving iodine supplementation (seven cases). The remaining 399 women with a total of 930 urinary samples were analysed for UICs. Median with interquartile range and mean (±SD) for each trimester are presented in Table 1. Notably, UICs were relatively low compared with the reference levels of adequacy (250–499 mcg L^{-1}), and not significantly different among the three trimesters, although UICs had a tendency to be higher in the second and third trimester when compared with those in the first trimester (Fig. 1). The median of UICs throughout pregnancy was only 150.67 mcg L^{-1}. The adequacy of iodine status in each trimester, categorized by WHO criteria, is presented in Table 2. Interestingly, based on the total number of collected samples, nearly half of all samples indicated iodine insufficiency and only approximately 2% showed excessive urinary iodine levels. Of 399 cases, if iodine status of each patient was represented by the means of their UICs derived from

Table 1. Median (interquartile range: IQR) and mean (±SD) of the urinary iodine concentrations in each trimester derived from 930 samples of 399 women

Trimester	*n*	Median	IQR	Mean	Standard deviation	ANOVA (repeated measures)
1	384	147.39	99.42–202.26	164.37	98.16	0.092
2	325	157.01	99.83–224.13	181.83	138.07	
3	221	153.07	106.10–225.85	180.50	133.09	
Total	930	150.67	101.54–213.74	174.30	122.00	

ANOVA, analysis of variance; SD, standard deviation.

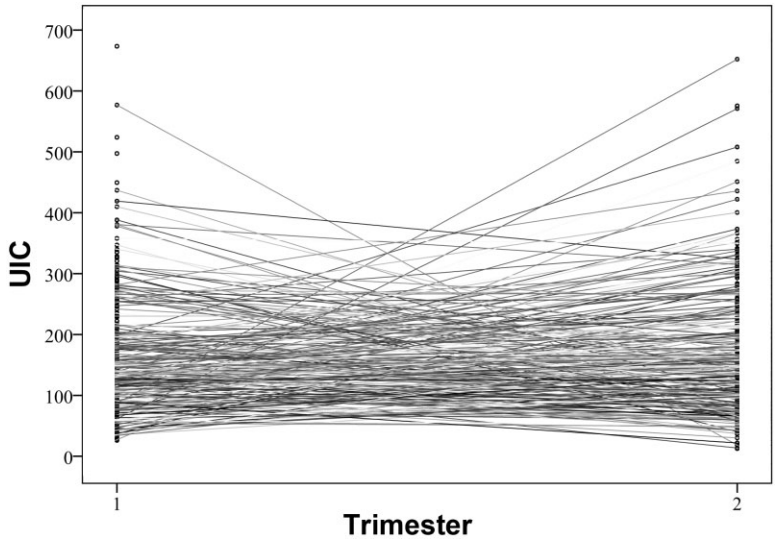

Fig. 1. Scatter lines of urinary iodine levels of patients in the first and second trimester. UIC, urinary iodine concentration.

Table 2. Adequacy of iodine status in each trimester based on the total number of 930 collected samples from 399 women

Pattern of adequacy in each trimester	Number of cases (%)
Insufficiency in all trimesters	82 (20.55%)
Insufficiency in the first two trimesters with dropout in the third trimester	50 (12.53%)
Insufficiency in the first trimesters with dropout in the last two trimesters	34 (8.52%)
Sufficiency in all trimesters	103 (25.81%)
Sufficiency in the first two trimesters with dropout in the third trimester	72 (18.05%)
Sufficiency in the first trimesters with dropout in the last two trimesters	35 (8.77%)
Other patterns (sufficiency in one or two trimesters and insufficiency in the others, sufficiency in one trimester/insufficiency in another one and dropout in the other)	23 (5.76%)

each trimester, 43.6% (174 women) had iodine insufficiency and 56.4% (225 women) had iodine sufficiency. The group with iodine sufficiency included a group of proper adequacy 43.4% (173), above requirement 12.0% (48) and excessive levels 1.0% (4). The complete data of pregnancy outcomes were available in 390 women, 171 in the group with iodine insufficiency and 219 in the group with iodine sufficiency. The baseline characteristics of women in the two groups were comparable as shown in Table 3. Frequencies of most pregnancy outcomes were not significantly different as presented in Table 4. Never-

Table 3. Comparisons of baseline characteristics of pregnant women with iodine insufficiency and those with iodine sufficiency

	Insufficiency (*n*: 171)	Sufficiency (*n*: 219)	*P*-value
Maternal age (years) mean ± SD	28.26 ± 5.50	28.13 ± 4.86	0.812
Maternal BMI mean ± SD	23.56 ± 2.98	23.34 ± 3.31	0.494
Number of ANC visits mean ± SD	10.64 ± 2.65	10.31 ± 3.42	0.288
Gestational age (days) mean ± SD (first sampling)	11.58 ± 4.36	11.30 ± 4.32	0.473
Gestational age (week) mean ± SD (second sampling)	18.68 ± 4.33	18.19 ± 4.05	0.063
Gestational age (week) mean ± SD (third sampling)	29.82 ± 5.34	29.43 ± 6.11	0.609
Parity (nulliparous/multiparous)	98/73	130/89	0.683
Income (high/low)	107/64	129/90	0.462
Education (high/low)	108/63	141/78	0.803
Religion (Buddhism/others)	165/6	202/17	0.077
Medical disease (absence/presence)	159/12	206/13	0.665

ANC, antenatal care; BMI, body mass index; SD, standard deviation.

Table 4. Associations between iodine sufficiency and adverse pregnancy outcomes

	Sufficiency *n* = 219; *n* (%)	Insufficiency *n* = 171; *n* (%)	RR (95% CI)	*P*-value
Gestational week at birth (mean ± SD)	38.73 ± 3.01	37.66 ± 2.35	–	<0.001
Birthweight (g) mean ± SD	3006.64 ± 620.44	2833.15 ± 564.92	–	0.005
Stillbirth	7 (3.2%)	2 (1.2%)	0.37 (0.08–1.74)	0.186
IUGR	20 (9.1%)	23 (13.5%)	1.47 (0.84–2.59)	0.177
Preterm birth	22 (10.0%)	30 (17.5%)	1.75 (1.05–2.92)	0.031
LBW	27 (12.3%)	34 (19.9%)	1.61 (1.02–2.57)	0.042
Low Apgar score 1 min	29 (13.2%)	15 (8.8%)	0.66 (0.37–1.19)	0.166
Low Apgar score 5 min	11 (5.0%)	5 (2.9%)	0.58 (0.21–1.64)	0.300
Antepartum haemorrhage	4 (1.8%)	6 (3.5%)	1.92 (0.55–6.70)	0.297
PIH	16 (7.3%)	7 (4.1%)	0.56 (0.24–1.33)	0.181
GDM	15 (6.8%)	21 (12.3%)	1.79 (0.95–3.37)	0.066
Caesarean delivery	53 (24.2%)	41 (24.0%)	0.99 (0.69–1.41)	0.959

CI, confidence interval; GDM, gestational diabetes mellitus; IUGR, intrauterine growth restriction; LBW, low birthweight; PIH, pregnancy-induced hypertension; RR, risk ratio; SD, standard deviation.

theless, the rate of PTB was slightly but significantly higher among women with iodine insufficiency, 17.5% vs. 10.0%, relative risk of 1.75, $P = 0.031$. Consequently, the rate of LBW was significantly higher in the group with iodine insufficiency, 19.9% vs. 12.3%, relative risk of 1.61, $P = 0.042$. Accordingly, mean gestational age at delivery of women in the group with iodine insufficiency was slightly but significantly lower than in the group with iodine sufficiency (37.66 vs. 38.73 weeks, $P < 0.001$). Likewise, mean

Table 5. Adjusted odd ratios for the risk of preterm birth and low birthweight derived from logistic regression analysis

Outcomes		Preterm birth (<37 week)		Low birthweight	
Potential risk factors	*n*	*P*-value	Adjusted odd ratios (95% CI)	*P*-value	Adjusted odd ratios (95% CI)
Maternal age		0.992	1.00 (0.934–1.07)	0.083	0.95 (0.89–1.01)
Number of ANC		<0.001	0.79 (0.71–0.87)	<0.001	0.78 (0.70–0.86)
Inadequate					
Adequate					
Income		0.570	0.81 (0.40–1.67)	0.892	1.05 (0.53–2.08)
High	236				
Low	154				
Education		0.701	0.87 (0.42–1.80)	0.688	1.15 (0.58–2.29)
High	249				
Low	141				
Religion		0.827	1.15 (0.32–4.19)	0.517	1.52 (0.43–5.32)
Buddhism	367				
Others	23				
Medical disease		0.947	0.96 (0.26–3.52)	0.282	0.43 (0.09–1.99)
Present	25				
Absent	365				
PIH		0.025	3.56 (1.17–10.80)	<0.001	7.19 (2.39–21.60)
Present	23				
Absent	367				
APH		0.621	1.53 (0.29–8.21)	0.829	0.83 (0.14–4.73)
Present	10				
Absent	380				
Iodine status		0.004	2.69 (1.38–5.24)	0.003	2.66 (1.40–5.05)
Insufficiency	171				
Sufficiency	219				
Parity		0.185	0.60 (0.29–1.27)	0.005	0.35 (0.17–0.73)
Nulliparous	228				
Multiparous	162				
BMI		0.392	1.05 (0.94–1.16)	0.337	1.05 (0.95–1.16)

ANC, antenatal care; APH, antepartum haemorrhage; BMI, body mass index; CI, confidence interval; PIH, pregnancy-induced hypertension.

birthweight in the group with iodine insufficiency was significantly lower (2833 ± 565 vs. 3007 ± 620 g, $P = 0.005$). Interestingly, the rate of FGR was not significantly associated with iodine status. However, if severe iodine insufficiency was defined as UIC of lower than 100 mcg L^{-1}, the rate of FGR was significantly higher in the group with iodine insufficiency, 13/68 (19.1%) vs. 30/322 (9.3%), relative risk 2.05 (95% CI: 1.13–3.72), $P = 0.031$.

To further evaluate the association between iodine status and the rate of PTB as well as LBW, logistic regression analysis was performed to control other confounders as presented in Table 5. It was found that iodine status was an independent factor accounting for an increased risk of preterm delivery and LBW. Additionally, the number of antenatal care visits and occurrences of PIH was also a significant risk factor of PTB and LBW.

Discussion

Unlike other previous studies that focused on an association between maternal iodine status and fetal or neonatal thyroid function and neurological development, this study was aimed at identifying the prevalence of iodine insufficiency and its effect on adverse pregnancy outcomes. Based on this study, the prevalence of iodine insufficiency was higher than expected and it seemed unethical not to supplement iodine during pregnancy in this geographical area and it

might be impossible to further conduct a study like this as we could not keep them un-nourished ethically. The policy of universal salt iodization has been launched in Thailand for many years (ICCIDD 2009, 2013). However, our data indicated that the policy had not perfectly worked, although the reasons for such an observation remain unclear, and attention to this problem must be paid seriously.

The prevalence of maternal iodine insufficiency greatly varied from countries to countries. Therefore, each geographical area should have its own data that can lead to different approaches for widely control or national policy. For example, our study suggests the necessity of urgent solution for such a high rate of iodine insufficiency among pregnant women in the northern part of Thailand. This is due to the fact that other than adverse impact on pregnancy outcomes it has been established that maternal iodine insufficiency can have long-term adverse impact on fetal neurological development (Cao *et al*. 1994; Delange 2001; Zimmermann 2011, 2012; Hynes *et al*. 2013), which could not be ameliorated by iodine supplementation during childhood. Note that our conventional antenatal care did not routinely supplement iodine to pregnant women and the women who took iodine supplementation were excluded from analysis. Therefore, the iodine status in this study might not represent the true status of all our obstetric population. Nevertheless, high percentage of women with iodine insufficiency in this study could reflect the baseline of iodine status in our population and indicates that guidelines for iodine intake and monitoring during pregnancy are needed.

Some previous studies indirectly suggested that iodine insufficiency may adversely affect birthweight or fetal growth (Zimmermann 2011; Pearce 2012). In China, Cao *et al*. (1994) reported reduction in the rate of microcephaly from 27% to 11% with iodine repletion of pregnant women with severe iodine insufficiency. In Algeria, Chaouki & Benmiloud (1994) reported that oral administration of lipiodol before or during the first trimester of pregnancy normalized thyroid function in newborn babies and mothers, increased placental and birthweight, and reduced the frequency of iodine insufficiency. In Spain, Alvarez-Pedrerol *et al*. (2009) suggested that iodine status during pregnancy might be related to prenatal growth in healthy women, in particular the babies of mothers with urinary iodine below 50 mcg L^{-1}. Nevertheless, there have been some conflicting data. Mason *et al*. (2002) reported that the use of iodated salt was related to birthweight in Sri Lanka and in the Philippines, where iodized oil capsules given during pregnancy had a negative effect when used with high levels of iodine in salt. To the best of our knowledge, the impact of maternal iodine insufficiency on adverse pregnancy outcomes other than thyroid problems is still inconclusive. Unlike previous reports, this study suggested that iodine insufficiency might have minimal effect on fetal growth but it could rather predispose to PTB and LBW. We have noted that a significantly higher rate of FGR was observed only when UIC was lower than 100 mcg L^{-1}. However, it is possible that insufficiency of other nutritional factors, which possibly tended to be more prevalent among women with iodine insufficiency, might have confounded and accounted for such adverse outcomes.

The weakness of this study might include (1) no evaluation of other nutritional factors apart from iodine, which could have been confounders for adverse pregnancy outcomes; (2) neither assessment of fetal and neonatal thyroid function nor long-term follow-up for neurological development. The strength of this study included (1) adequate sample size of the cases with iodine insufficiency to assess the adverse pregnancy outcomes, although the total number of cases did not seem to be large; (2) prospective nature of the cohort study, together with the fact that the results of iodine status were blinded to the doctors who assessed the pregnancy outcomes; and (3) the measurement of the UIC was based on a highly reliable laboratory methods.

In conclusion, this study provides insights on iodine status during pregnancy as follows: (1) in northern Thailand, a great number of pregnant women who were not taking iodine supplements had a median UIC less than 150 mcg L^{-1}; (2) urinary iodine levels had a tendency to increase during the second trimester, when compared with those in the first trimester, although not significantly different; (3) iodine insufficiency was associated with an increased risk of PTB as well as LBW; (4) severe iodine insufficiency

(<100 mcg L^{-1}) increased the risk of FGR, although such an effect was probably minimal; and finally (5) iodine insufficiency was unlikely to increase the risk of other common adverse pregnancy outcomes such as PIH or antepartum haemorrhage.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

CC: Proposal development, Data collection, Manuscript writing. PL: Laboratory analysis (urinary iodine concentration measurements). KT: Proposal development, Data collection. TT: Data analysis, Manuscript editing.

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