Correlation between Iodine Supplement in Pregnancy and Neonatal TSH Level

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Objective: *To evaluate the correlation of neonatal thyroid stimulating hormone (TSH) between iodine supplemented and no-iodine supplemented pregnant women.*
Material and Method: *The present study was a prospective randomized controlled trial (RCT) that was taken at ANC unit, labor ward, and neonatal unit at Siriraj Hospital, Mahidol University, Bangkok, Thailand. Two hundred sixty six pregnant women were recruited between June 15, 2015 and July 31, 2016. They were randomized into two groups, iodine and no-iodine supplemented group.*
Results: *No statistical significant of demographic data, original habitant areas, and adverse neonatal outcomes including preterm labor and low birthweight, of the pregnant patient between these two groups. Only the median value of neonatal TSH level was 3.44 and 3.95 mIU/l in iodine and no-iodine supplemented group, respectively, which was statistically significant different between the two groups (p-value <0.05). However, there were no clinical difference between the two groups.*
Conclusion: *The present study presented that there was statistical significant difference of the median value of neonatal TSH level between two groups of iodine and no-iodine supplement pregnant women. Even if there was no clinically significant difference and none of the newborn was diagnosed of hypothyroidism, iodine supplementation in all pregnant women should be of concerned. A large prospective study would benefit the iodine implementation of pregnant women in Siriraj Hospital.*

Keywords: *Iodine supplementation, Neonatal TSH, Hypothyroidism*

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Iodine is an important substance of thyroid hormones that have a major role in cell metabolisms, myocardial, hepatic, and muscle functions, and necessary for cell growth especially for neurons. Thyroid hormones deficiency during pregnancy may result in neonatal hypothyroidism, childhood cretinism, or adverse pregnancy outcomes such as miscarriages and preterm labor[1-6].

From WHO recommendations, pregnant women should receive iodine at least 250 mcg/day. The numbers of iodine deficiency in pregnant women were reported mainly in Africa and Asia[7]. From the national survey in 2013, Thailand had iodine deficiency as a major problem in pregnant Thai women. Nearly half of all iodine deficiency pregnant women were distributed in the North and the Northeast of Thailand[8].

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The screening of neonatal hypothyroidism and phenylketonuria with the laboratory tests of thyroid stimulating hormone (TSH) and phenylketonuria (PKU) level have been adopted by the national policy in Thailand. The Pediatric Genetic Division of the Pediatrics Department, Faculty of Medicine Siriraj Hospital, 2013 has reported the abnormal high TSH level of 0.17%. However, only 0.02% of neonates in this group were diagnosed as hypothyroidism[9]. Moreover, there was no medical record definitely presented of maternal iodine supplementation during pregnancy because the prescription of iodinized medication was up to the physicians' opinion.

Although there is the policy of iodine supplementation in pregnant women, iodine-contained medication is still insufficiently produced by the Ministry of Health. Iodine admixed preparation by other company is also expensive, which cannot be affordable by the patient with low socioeconomic status. Although Thai food contained some iodine such as fish sauce, chili sauce, and seafood, Thai pregnant women still need iodine supplement during pregnancy.

The present research was set to study Thai pregnant women for the necessity of iodine-contained medicated supplement during pregnancy.

Material and Method

The present study was approved by the Siriraj Institutional Review Board, the institute's Ethic Committee (COA No. SI 524/2014). This prospective randomized controlled trial (RCT) was performed between October 2014 and July 2016. All singleton pregnant women, older than 18 years with gestational age less than 18 weeks on the day of starting participation were included. The exclusion criteria were the patients who have contraindication to use iodine, previously receive other iodine-contained drugs, multifetal pregnancy, pregnancy with fetal anomaly, and pregnancy with abnormal thyroid function (hyperthyroidism or hypothyroidism).

Two hundred sixty six pregnant women were recruited and divided into two groups, 133 in each group, by block randomization (block of ten) (i) iodine-contained ferrous tablet and (ii) no iodine-contained ferrous tablet. Patient's demographic data were obtained including age, pre-pregnant body weight, height, occupation and incomes, habitat, socio-economic status, parity, antenatal care (ANC) history, and medications received during pregnancy.

All pregnant women were treated as standard care as others, such as gestational diabetes mellitus (GDM) screening, thalassemia screening, ultrasonography, and other indicated fetal surveillances. In anemic patients (hematocrit was not exceeded 33%), the iron supplement by adding FeSO4 tablets was prescribed.

The primary objective was to find some correlations between neonatal TSH levels at 48-hour of life in iodine supplemented and no-iodine supplemented group. By the reference cut-off value of abnormal high TSH level was 12 mIU/L, refer to laboratory reference of Genetics Division, Pediatrics Department Siriraj Hospital.

All descriptive data were analyzed by descriptive statistics and unpaired t-test or Mann-Whitney U test was used to analyze the correlation of the data, neonatal TSH level. The data had statistical significant at *p*-value less than 0.05.

Results

Of the total 266 pregnant women initially recruited, four women left the study due to delivered at other hospitals, moving to another province and a fetal death from spontaneous ruptured of umbilical vessels.

The demographic data and neonatal outcomes were presented in the Table 1-3. The general demographic data including mean age, parity, body weight, height, body mass index (BMI), gestational age at first ANC and started medication, occupation, education, and income were no statistically significant difference between two groups (*p*-value <0.05). The habitat was also similar in two groups.

For the neonatal outcomes; preterm birth rate of the patients with iodine and non-iodine supplemented groups were 6.8% and 7.5% and the rate of low birth weight of those patients were 6.1% and 9%, respectively. No statistically significant difference was detected between the patients in both groups. Mean gestational age at delivery were 38.1 and 38.2 weeks and mean neonatal birth weight were 3,068.6 and 3,101.0 grams, respectively, between the patients in both groups with no statistically significant difference (Table 3).

According to the small population in each group, which resulted in the abnormal distribution of the result, median value of TSH level was used to

Table 1. Demographic data of the study groups

Demographic data	Iodine supplemented group (n = 134) mean (SD)	No-iodine supplemented group (n = 132) mean (SD)	*p*-value[+]
Age	29.8 (5.7)	30.1 (5.8)	0.64
Body weight	54.9 (10.4)	55.3 (11.5)	0.75
Height	158.2 (6.2)	158.6 (5.6)	0.59
BMI	21.9 (3.9)	22.0 (4.3)	0.93
GA at 1st ANC	10.1 (3.1)	10.8 (3.6)	0.08
GA start medication	14.8 (2.1)	14.8 (2.1)	0.82

BMI = body mass index; GA = gestational age; ANC = antenatal care
[+] t-test

Table 2. Demographic data of the study groups

Demographic data	Iodine supplemented group (n = 134), n (%)	No-iodine supplemented group (n = 132), n (%)	*p*-value[+]
Parity			0.39
1	45 (34.1)	52 (38.8)	
2	57 (43.2)	47 (35.1)	
3	25 (18.9)	25 (18.7)	
4	5 (3.8)	8 (6.0)	
5	0 (0)	2 (1.5)	
Occupation			
Housewife	21 (15.9)	17 (12.7)	
Farmer	0 (0)	1 (0.7)	
Government officer	11 (8.3)	16 (11.9)	
State enterprise officer	3 (2.3)	4 (3.0)	
Laborer	71 (53.8)	73 (54.5)	
Merchant	16 (12.1)	18 (13.4)	
Others (student, business owner, unemployed)	10 (7.6)	5 (3.7)	
Income (bath)			0.44
<10,000	17 (12.9)	16 (11.9)	
10,000 to 29,999	79 (59.8)	91 (67.9)	
30,000 to 49,999	22 (16.7)	19 (14.2)	
>50,000	14 (10.6)	8 (6.0)	
Education			0.68
Primary school	2 (1.5)	3 (2.2)	
Secondary school	52 (39.4)	58 (43.3)	
Bachelor of arts and higher degree	78 (59.1)	73 (54.5)	

[+] Chi-square test

Table 3. Neonatal outcome

Neonatal outcome	Iodine supplemented group (n = 134) mean (SD)	No-iodine supplemented group (n = 132) mean (SD)	*p*-value
GA at delivered	38.1 (1.6)	38.2 (2.2)	0.93
Neonatal birth weight	3,068.6 (461.6)	3,101.0 (434.5)	0.56

GA = gestational age

Table 4. Incidence of preterm birth and low birth weight

	Iodine supplemented group (n = 134), n (%)	No-iodine supplemented group (n = 132), n (%)	*p*-value[+]
Preterm birth (GA <37 weeks)	9 (6.8)	10 (7.5)	0.84
Extremely preterm(<28 weeks)	0 (0)	0 (0)	
Very preterm (28 to <32 weeks)	2 (1.5)	0 (0)	
Moderate to late preterm (32 to <37 weeks)	7 (5.22)	10 (7.5)	
Low birth weight (birth weight <2,500 g)	8 (6.1)	12 (9.0)	0.38
Extremely low birth weight (<1,000 g)	0 (0)	0 (0)	
Very low birth weight (1,000 to <1,500 g)	3 (2.24)	0 (0)	
Low birth weight (1,500 to <2,500 g)	5 (3.73)	12 (9.0)	

GA = gestational age

[+] Chi-square test

compare in both groups. Neonatal TSH level of the patients in iodine supplemented group was 3.44 mIU/L which was lower than those of the patients in non-iodine supplemented group, 3.95 mIU/L. There was statistical significant difference between the two groups (*p*-value = 0.04) (Table 5).

When we correlated the result of neonatal TSH level to the clinical of neonatal hypothyroidism,

Table 5. Showed median of neonatal TSH in two groups

Groups	n	Median of neonatal TSH (mIU/ml), (range)	*p*-value+
Iodine supplemented group	130	3.44 (0.66 to 11.30)	0.04
No-iodine supplemented group	131	3.95 (1.31 to 10.60)	

TSH = thyroid stimulating hormone
+Mann-Whitney U test

we found no clinically significant difference. None of the neonates were diagnosed hypothyroidism nor abnormal high TSH level.

Discussion

The present study focused on the correlation between iodine supplement during ANC and neonatal TSH level at 48-hour of life. We found that median neonatal TSH level in iodine supplemented group was lower than those in non-iodine supplemented group. However, there was no clinical statistically significant difference. There were few reasons to explain no clinical statistically significant difference.

Firstly, we did not measure baseline iodine status before given iodine supplement. Even though, the national survey data showed that most of Thai pregnant population had iodine deficiency but the present study conducted in the capital city of Thailand, Bangkok, which had plenty sources of iodine supplemented food. We might add iodine to non-iodine deficient pregnant women. Secondly the non-iodine supplemented group might receive iodine supplement from dietary which made total iodine intake exceeded 250 mcg per day, resulting in normal TSH level.

From the study of Sukkhojaiwaratkul et al[10], which was taken in Thailand, they studied maternal urine iodine concentration throughout the gestation and screening for congenital hypothyroidism by TSH level in cord blood. The final conclusion of their study also presented similar result as ours.

The study of Nøhr and Laurberg[11], in Denmark, found that there was higher TSH level of neonates in iodine supplemented group. Their study was taken in area of mild iodine deficiency, they concluded that the iodine supplementation in mothers who lived in mild iodine deficiency area may transient inhibited thyroid function in neonates, which may cause neonatal hypothyroidism. However, they also mention that iodine supplementation during pregnancy is still benefit to brain development.

The strength of our study was the RCT. The sequence generation and allocation were good enough, resulting in no significant different in demographic data between the two groups. However, our study had some limitations as following: some foreign babies were loss to screen the TSH level due to unaffordable of the screening cost, incompleteness of iodine supplementation, lack of assessment in medication adherence in both groups and no basic data of the iodine status before participating in our study.

For the strong information prior to the added up benefit of iodine supplement during ANC for all pregnant women in Siriraj Hospital, a larger prospective RCT should be performed. Baseline iodine status should be evaluated before giving iodine supplement. The dietary intake should also be in the result interpretation.

Conclusion

The median value of neonatal TSH level between two groups of iodine and no-iodine supplement in pregnant women was statistical significance. Although there was no clinically significant, iodine supplementation in all pregnant women should be concerned to promote brain development. Large prospective RCT trial is still benefit for the iodine implementation of pregnant women in Siriraj Hospital.

What is already known on this topic?

From the previous studies, iodine is essential for fetal brain and thyroid development and recommended for all pregnant women. However, the implementation of iodine in pregnant women cannot apply for all centers, especially in Siriraj Hospital, the tertiary center in Thailand. The believing of sufficient iodine intake during pregnancy leads to unconcern for iodine supplementation during pregnancy in Siriraj Hospital. The objective of this study was to evaluate the TSH level of neonates between iodine and non-iodine supplement in mothers during pregnancy.

What this study adds?

The result of the study presented the statistical significant difference of the median value of neonatal TSH level between iodine and non-iodine supplement. Even though there was no clinical significant difference

of hypothyroidism in neonates, iodine is still beneficial for brain development. This study indicated that iodine supplementation affected to TSH level in neonate and should be concerned for implementation in all pregnant women, especially in Siriraj Hospital. Larger study is needed for confirm the benefit of iodine implementation.

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Potential conflicts of interest

None.

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ความสัมพันธ์ของการได้รับยาเม็ดเสริมไอโอดีนในหญิงตั้งครรภ์กับระดับ TSH ของทารกแรกเกิด

พูนสุข ด่านดำรงรักษ์, สายฝน ชวาลไพบูลย์

วัตถุประสงค์: *ศึกษาความสัมพันธ์ของการได้รับยาเม็ดเสริมไอโอดีนในหญิงตั้งครรภ์และระดับ TSH ในทารกแรกคลอด*

วัสดุและวิธีการ: *เป็นการศึกษาไปข้างหน้า โดยคัดหญิงตั้งครรภ์ทั้งหมด 266 ราย ที่ฝากครรภ์และมีความตั้งใจที่จะคลอดที่โรงพยาบาลศิริราช และแบ่งออกเป็นสองกลุ่มโดยใช้การสุ่ม โดยเลือกให้ยาเม็ดที่มีธาตุเหล็ก และยาเม็ดที่มีธาตุเหล็ก วิตามิน รวมทั้งไอโอดีนเป็นส่วนประกอบ แบ่งเป็นกลุ่มละ 133 ราย จากนั้นเก็บข้อมูลพื้นฐานของกลุ่มตัวอย่างในระหว่างฝากครรภ์ และเก็บตัวอย่างเลือดจากส้นเท้าทารกส่งตรวจคัดกรองภาวะพร่องไทรอยด์เมื่อทารกอายุครบ 48 ชั่วโมงหลังคลอด นำข้อมูลที่ได้มาแปลผลด้วยสถิติเชิงบรรยาย สถิติเชิงเปรียบเทียบ*

ผลการศึกษา: *ข้อมูลพื้นฐานของกลุ่มตัวอย่างทั้งสองกลุ่ม เช่น อายุ อายครรภ์ น้ำหนักทารกแรกคลอด นั้นไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (ที่ค่า p-value <0.05) แต่กลุ่มที่ได้รับยาเสริมไอโอดีน มีระดับ TSH ที่ต่ำกว่าอย่างมีนัยสำคัญทางสถิติ โดยมีค่า TSH เท่ากับ 3.44 และ 3.95 mIU/L ในกลุ่มทารกของหญิงตั้งครรภ์ที่ได้รับยาเม็ดเสริมไอโอดีน และไม่ได้ยาเม็ดเสริมไอโอดีนตามลำดับ (p-value <0.05) แต่ไม่มีนัยสำคัญทางคลินิก*

สรุป: *แม้ว่าการศึกษาจะพบว่าการให้ไอโอดีนจะช่วยให้มีค่า TSH ดีขึ้น และไม่มีทารกที่ได้รับการวินิจฉัยภาวะพร่องไทรอยด์ก็ตาม ยังควรส่งเสริมให้มีการให้ไอโอดีนในหญิงตั้งครรภ์เพื่อลดภาวะขาดไอโอดีน ที่สามารถส่งผลกระทบต่อการตั้งครรภ์และการพัฒนาของสมองทารกในระยะยาว*