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Research Article

Relationship between Different Iodine Status during Pregnancy and Infantile Physical Development in China

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Abstract

Background: Maternal iodine status is an important public health issue worldwide because it is unequivocally important for offspring's growth and development. While the effect of mild iodine deficiency/excessive during pregnancy on their infants' physical growth is still uncertain and further studies are needed to conform it.

Methods: This prospective study used Tianjin and Wuqiang registers of pregnant women and their 18-24 months infants, 2016 to 2018. Blood and urine samples from each mother-infant pair were collected to determine thyroid function and UIC. Infants' weight, length and head circumference were measured.

Results: A total of 469 mother-infant pairs were enrolled, including 245 boys (52.2%) and 224 girls (47.8%). Maternal and infants' median UIC was 161 (111, 251) μg/L and 217 (121, 361) μg/L, both suggesting iodine sufficiency according to WHO/UNICEF /ICCIDD-recommended criteria. Only the head circumference for age (HFA) Z-scores in infants with UIC 100-149μg/L during pregnancy was above zero, and higher than those with UIC<100μg/L and 150-249μg/L (all $P<0.05$). No differences were found in Z-scores of length-for-age, weight-for-age and weight-for-length in infants with different maternal UIC during pregnancy, and no association was found between maternal thyroid function and infants' physical growth.

Conclusions: The HFA Z-score was higher in infants with maternal UIC 100-149 μg/L, rather than 150-249μg/L, which imply that the criteria recommended by WHO/UNICEF/ICCIDD may be a little high for Chinese pregnant women in such background of iodine nutrition.

INTRODUCTION

Iodine is an essential microelement to maintain human health [1, 2]. Especially, during the first 1,000 days of life, adequate iodine intake is unequivocally important for infantile physical and brain development [3]. The iodine requirement increases during pregnancy due to the transfer of iodine to the fetus and increased maternal thyroid hormone synthesis [4]. Therefore, pregnant women are highly vulnerable to iodine deficiency.

Approximately 90% of the iodine ingested by the body is excreted in the urine, so urine iodine is a good indicator of recent iodine intake. Median urinary iodine excretion is a recommended biomarker for monitoring daily iodine intake in specific populations [5,6]. World Health Organization (WHO)/ United Nations International Children's Emergency Fund (UNICEF)/ International Council for Control of Iodine Deficiency Disorders (ICCIDD) recommended an adequate median urine iodine concentration (UIC) of 150-249μg/L for pregnant women, higher than that for reproductive women (100-199μg/L) [7]. The latest national iodine deficiency disease surveillance reported that the iodine status of residents in China was appropriate. But in six provinces and cities, the median UIC for pregnant women was lower than 150μg/L, indicating mild iodine deficiency [8].

Iodine deficiency during lactation will affect the iodine nutritional status and thyroid function of infants, and even negatively affect their growth and development [9]. But, evidence on the effects of iodine status during pregnancy on infantile growth and development is limited. Severe iodine deficiency during pregnancy can lead to a series of adverse pregnancy outcomes, including thyroid dysfunction, miscarriage, and stillbirth, even congenital cretinism and growth retardation in infants [3,10]. However, current research on the relationship between mild iodine deficiency in pregnancy and physical development is inconclusive. Some studies reported adverse effects of mild iodine deficiency during pregnancy on infantile growth and development [11,12]. However, results from other cohort studies have shown no differences in infantile physical development between mothers with mild iodine deficiency [9,13].

Due to the success of salt iodization programmer commonly implemented in China, public health attention has shifted to mild-to-moderate iodine deficiency, which is still prevalent in some areas, especially among pregnant women. Currently, there are few and controversial studies on the relationship between iodine status during pregnancy and physical development. This study was aimed to investigate physical development of infants at 18-24 months old under different maternal iodine status during pregnancy and evaluate the relationship between iodine status during pregnancy and physical development of infants in China. This prospective study compared different maternal iodine levels in relation to infant physical development.

MATERIALS AND METHODS

Subjects and Design

This study is a part of an ongoing prospective study conducted in Tianjin and Wuqiang, which was designed to explore the relationship between iodine status during pregnancy and neonatal Thyroid stimulating hormone (TSH) and infants' physical growth at 18-24 months old. These two areas are adjacent, with similar geography, culture, dietary habits, and food and water iodine concentration. Wuqiang is a county in Hebei Province, where the iodine content in drinking water is <15.0µg/L and both crude salt (non-iodized) and refined iodized salt are consumed. In a pilot study among 77 pregnant women in Wuqiang the 24-h UIC was 108 (69, 163) µg/L, and 67.6% of the UIC values were <150µg/L. Therefore, Wuqiang was chosen as a mildly iodine-deficient region for this study. Tianjin, where iodized salt is the main source of iodine, is iodine sufficient (8).

All subjects were recruited from the Departments of Obstetrics in Tanggu Maternity Hospital, Tianjin and the Wuqiang Center of Diseases Prevention and Control, Hebei from March 2016 to June 2018. All pregnant women presenting for their routine antenatal care during pregnancy were invited to participate in our study after a general description of the project. The gestational week was determined based on the results of the ultrasound examination of the pregnant woman's abdomen or the time of the last menstruation. Women aged 20-35 years with no previous history of thyroid disease, no use of thyroid-related medications, and no other chronic diseases were eligible for inclusion. Pregnant women who had lived in the local area for less than 5 years or who were using iodine supplements were excluded. Pregnant women were recalled back 18-24 months after delivery and were investigated, until to December 2019, 469 mother-infant pairs were recruited. All research protocols were approved by the Medical Ethics Committee of Tianjin Medical University, all procedures performed in the study were in accordance with the ethical standards of the committee and with the 1964 Helsinki declaration. All participants provided written informed consent after research protocols were carefully explained to them (Ethical approval number: NCT03710148).

Data and Sample collection

Subjects during pregnancy were asked to complete a questionnaire to obtain information including age, gestational week, height and weight, etc. Maternal spot urine was obtained at enrollment from 8:00 to 11:00 AM after an overnight fast during an antenatal hospital visit. Dried blood spot samples were obtained from neonatal heels and infantile fingertips at birth and 18-24 months old, respectively. Infantile length and weight were measured at birth and 18-24 months old, and head and bust circumstance were measured only at 18-24 months old. Z-scores were calculated by (X-M)/S, M represents Reference standard median by WHO, S represents standard deviation, the physical growth of infants was categorized based on criteria of Z-scores recommended by WHO, <-2 is extremely delayed, <-1 is moderately delayed, <0 is slightly delayed, >0 is above the normal level, >1 is well developed, >2 is extremely developed. All samples were frozen at -80°C for assay within 2 weeks.

Analysis of urine samples & Categorization of UIC

UIC was analyzed by Inductively Coupled Plasma Mass Spectrometry (ICP-MS, Thermo Fisher Scientific iCAPTMQ, Germany) in the Tianjin Key Laboratory of Environmental Nutrition and Population Health. Based on the distribution of maternal UIC and WHO criteria, pregnant women were divided into 4 groups: <100µg/L (moderate deficiency), 100-149µg/L (mild deficiency), 150-249µg/L (sufficiency), >250µg/L (above requirements) in this study.

Determination of heel/fingertip TSH

Infants' heel/fingertip blood spot samples were collected on filter papers by skilled nurses at 72 hours after birth. All the samples were sent to the Tianjin Maternal and Child Health Center for analysis. Dried blood spot TSH was measured using dissociation-enhanced fluor-immunoassay.

Statistical analysis

All statistical analyses were performed using SPSS25.0 (IBM, Inc., New York, NY, USA), and Microsoft Excel (Win10 2016). The Kolmogorov-Smirnov method was used to test data distribution normality. Normally distributed data were presented as mean ± SD, and skewed data are presented as median (interquartile range). Difference in basic information between boys and girls was analyzed by t test or Kruskal-Wallis test. Difference in Z-scores, fingertip TSH and UIC of infants were analyzed via one-way ANOVA or nonparametric test. Significance was set at P<0.05 (two-tailed).

RESULTS

Demographic characteristic of infants at 18-24 months

Totally, 469 mother-infant pairs were enrolled in this study. The UIC of mother during pregnancy were 161 (111, 251) μg/L, indicating adequate iodine nutrition according to the WHO-recommended criteria of the UIC in pregnant women (data not shown). The basic information of their neonates was described in Table 1. Birth weight in female neonates was lower than that in male neonates (P=0.001), and the length-for-age (LFA) and weight-for-length (WFL) Z-scores were lower than those in male neonates (P<0.05). The median TSH levels of neonates were 3.1 (1.7, 4.5) mIU/L, no difference was found between boys and girls.

Pregnant women were recalled back 18-24 months after delivery, the average age of infants was 20.9 ± 3.0 months. Present weight, head circumference and bust in girls were lower than boys (P<0.001), no difference in gender of present length was found (P=0.231), and the corresponding WFL Z-scores in girls was also lower, while the LFA Z-scores in girls was higher than boys (P=0.007), differed from the trend of present length. The UIC in infants at 18-24 months was 217 (121, 361) μg/L, indicating adequate iodine nutrition. Both UIC and fingertip TSH in infants were not found difference between boys and girls (P>0.05).

UIC-specific difference of physical growth of infants

Based on the WHO-recommended criteria of the UIC during pregnancy, maternal UIC were divided into 4 groups (Table 2). No difference in birth length, weight, LFA Z-scores, weight-for-age (WFA) Z-scores and WFL Z-scores in neonates was found among different maternal UIC groups (all P>0.05). At 18-24 months after delivery, similar trends were found. Only head-for-age (HFA) Z-scores in UIC within 100-149μg/L during pregnancy was above 0, and it was highest (P=0.010), rather than 150-249μg/L, which was recommended by WHO as the criteria of sufficient iodine nutrition during pregnancy (Figure 1).

Both heel-blood and fingertip TSH showed no differences among different UIC groups (P>0.05). Weak but no significant difference in UIC in infants at 18-24 months was found (P=0.661).

Difference of physical growth in infants with different neonatal TSH

No infants were diagnosed as congenital hypothyroidism. Take 4.0mIU/L as the cut-off point, neonatal TSH was divided into 2 groups (Table 3). Compared to neonates with TSH<4.0mIU/L, no difference of birth length, weight, LFA Z-scores, WFA Z-scores and WFL Z-scores was found in neonates with TSH ≥4.0mIU/L (all P>0.05). At the age of 18-24 months, no significant changes also was found in length, weight, head circumference and bust in infants. LFA Z-scores in infants with neonatal TSH<4.0mIU/L was significantly higher than that in infants with neonatal TSH ≥4.0mIU/L (P=0.006), while no difference was found in WFA Z-scores, WFL Z-scores and HFA Z-scores between infants with neonatal TSH <4.0mIU/L and ≥4.0mIU/L (all P>0.05).

High neonatal TSH followed high fingertip TSH in infants at the age of 18-24 months (P<0.001), although fingertip TSH was within normal ranges. While, no impact was found in infants with neonatal TSH ≥4.0mIU/L on UIC in infants at 18-24 months was found (P=0.864).

DISCUSSION

Adequate iodine intake during pregnancy is vitally important to maintain the health of themselves and their offspring. A little much is too much, especially the iodine intake during pregnancy. Abnormal iodine nutrition during pregnancy has an adverse effect on the thyroid function of pregnant women and the brain development and physical growth of their infants [14,15]. UIC is most frequently used to evaluate the iodine nutrition of pregnant women and related criteria are defined by WHO/UNICEF/ICCIDD. The UIC during pregnancy in the present study was 161 (111, 251) μg/L, suggesting sufficient iodine nutrition, which was consistent with previous study in Tianjin (16). While part of iodine-deficient pregnant women still exists. The effect of iodine deficiency during pregnancy on physical growth lacked concern evidence, a few studies reported negative effect [15,17], but no effects were also reported [18]. Our study aimed to evaluate the effect of iodine nutrition during pregnancy on physical growth of infants.

Boys' physical and psychological development is earlier than girls' at the same age [19-21] which was also shown in our study, especially in LFA Z-scores at 18-24 months, although no difference

Table 1: describes the basic information of 469 newborns.

	Total (N=469)	Boys (n=245)	Girls (n=224)	*P*
Birth length, cm	51.1 ± 1.8	51.2 ± 2.0	50.9 ± 1.7	0.079
Birth weight, kg	3.4 ± 0.4	3.5 ± 4.4	3.3 ± 4.4	0.001
Birth LFA Z-scores	0.81 ± 0.97	0.68 ±1.03	0.95 ± 0.88	0.003
Birth WFA Z-scores	0.33 ± 0.99	0.33 ± 0.88	0.34 ± 1.09	0.968
Birth WFL Z-scores	−0.58 ± 1.05	−0.39 ± 1.13	−0.80 ± 0.91	<0.001
Neonatal TSH, mIU/L	3.1 (1.7, 4.5)	3.1 (1.8, 4.4)	3.0 (1.7, 4.5)	0.788
Age, months	20.9 ± 3.0	20.8 ± 2.9	21.0 ± 3.0	0.498
Present length, cm	85.2 ± 4.1	85.4 ± 4.2	84.9 ± 4.1	0.231
Present weight, kg	11.9 ± 1.5	12.2 ± 1.6	11.6 ±1.3	<0.001
Head, cm	47.2 ± 1.6	47.6 ± 1.6	46.8 ± 1.5	<0.001
Bust, cm	49.4 ± 2.8	49.9 ± 2.9	48.8 ±2.5	<0.001
LFA Z-scores	0.34 ± 1.12	0.20 ± 1.23	0.48 ± 0.97	0.007
WFA Z-scores	0.53 ± 1.03	0.53 ±1.15	0.53 ± 0.89	0.995
WFL Z-scores	0.48 ± 1.14	0.60 ±1.25	0.35 ± 1.00	0.018
HFA Z-scores	−0.17 ± 1.13	−0.26 ± 1.20	0.03 ± 1.04	0.064
Fingertip TSH, mIU/L	1.4 (0.9, 1.9)	1.4 (0.9, 2.0)	1.4 (0.9, 1.9)	0.778
UIC, μg/L	217 (121, 361)	241 (128, 374)	191 (114, 325)	0.121

Data were expressed as Mean ± SD or Median (P_{25}, P_{75}).
TSH, thyroid stimulating hormone; UIC, urinary iodine concentration; LFA, length-for-age; WFA, weight-for-age; WFL, weight-for-length; HFA, head-for-age.

Table 2: describes the physical development of newborns with different urinary iodine levels.

	UIC during pregnancy, μg/L				*P*
	<100	100-149	150-249	≥250	
Birth length, cm	51.3 ± 1.7	51.0 ± 2.0	51.1 ± 2.0	50.7 ± 1.9	0.383
Birth weight, kg	3.5 ± 0.4	3.4 ± 0.5	3.4 ± 0.5	3.3 ± .04	0.386
Birth LFA Z-scores	0.89 ± 0.88	0.81 ± 1.08	0.82 ± 1.04	0.65 ± 1.02	0.514
Birth WFA Z-scores	0.46 ± 0.88	0.35 ± 1.10	0.24 ± 1.10	0.23 ± 0.93	0.475
Birth WFL Z-scores	−0.46 ± 0.98	−0.56 ± 1.13	−0.75 ± 1.10	−0.54 ± 1.07	0.355
Neonatal TSH, mIU/L	3.7 (2.0, 4.9)	2.6 (1.6, 4.0)	3.1 (1.7, 4.7)	3.5 (1.7, 4.5)	0.195
Present length, cm	85.8 ± 4.6	85.0 ± 4.3	84.5 ± 3.7	84.9 ± 3.9	0.291
Present weight, kg	12.1 ± 1.6	11.9 ± 1.6	11.7 ± 1.3	11.7 ± 1.4	0.411
Head, cm	47.0 ± 1.7	47.5 ± 1.7	47.2 ± 1.5	46.9 ± 1.4	0.098
Bust, cm	49.3 ± 2.9	49.3 ± 2.5	49.3 ± 2.6	49.3 ± 2.9	0.999
LFA Z-scores	0.26 ± 1.14	0.41 ± 1.29	0.18 ± 0.97	0.38 ± 1.19	0.526
WFA Z-scores	0.47 ± 1.04	0.63 ± 1.13	0.45 ± 0.89	0.49 ± 1.02	0.652
WFL Z-scores	0.46 ± 1.1	0.56 ± 1.29	0.48 ± 0.99	0.39 ± 1.2	0.818
HFA Z-scores	−0.33 ± 1.19	0.23 ± 1.13	−0.06 ± 1.07	−0.23 ± 1.03	0.010
Fingertip TSH, mIU/L	1.3 (0.8, 2.2)	1.4 (0.9, 2.1)	1.3 (0.8, 1.8)	1.4 (1.0, 1.9)	0.770
UIC, μg/L	200 (115, 374)	215 (99, 389)	238 (140, 343)	252 (159, 388)	0.661
<100	14 (22.6%)	18 (25.7%)	16 (17.8%)	11 (15.3%)	0.398

Data were expressed as Mean ± SD or Median (P_{25}, P_{75}) or *n* (%).
UIC, urinary iodine concentration; TSH, thyroid stimulating hormone; LFA, length-for-age; WFA, weight-for-age; WFL, weight-for-length; HFA, head-for-age.

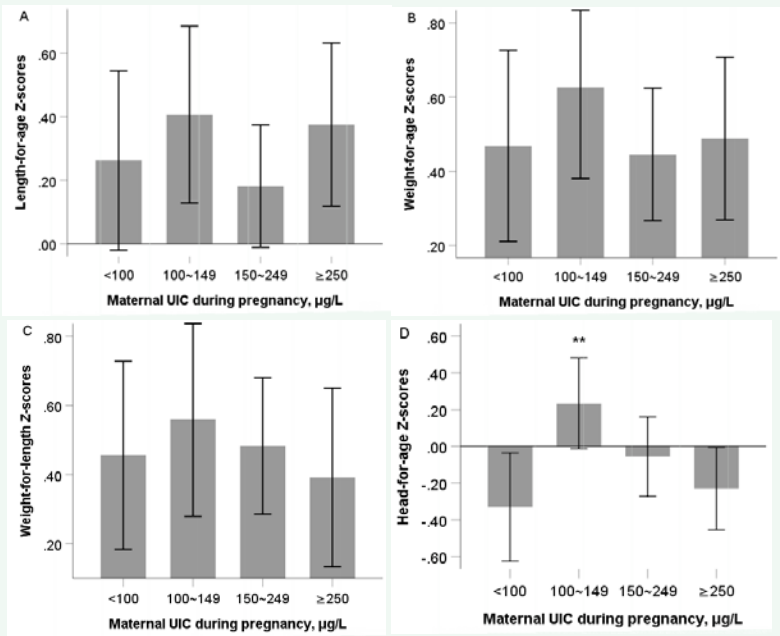

Figure 1 (A-D) Z-scores of length-for-age, weight-for-age, weight-for-length, and head-for-age of children in different levels of UIC during pregnancy. The bar chart describes the Z-score of length-for-age (A), weight-for-age (B), weight-for length (C), and head-for-age (D) of children in different levels of UIC during pregnancy.

Table 3: describes the effects of different neonatal TSH levels on children's physical development.

	Neonatal TSH, mIU/L		*P*
	<4.0	≥4.0	
Birth length, cm	51.3 ± 1.9	51.3 ± 1.7	0.951
Birth weight, kg	3.4 ± 0.5	3.4 ± 0.4	0.259
Birth LFA Z-scores	0.95 ± 0.99	0.96 ± 0.91	0.934
Birth WFA Z-scores	0.41 ± 1.01	0.29 ± 0.95	0.275
Birth WFL Z-scores	−0.67 ± 0.90	−0.85 ± 0.86	0.082
Present length, cm	85.5 ± 4.1	84.7 ± 4.2	0.094
Present weight, kg	12.0 ± 1.6	11.8 ± 1.4	0.517
head (cm)	47.4 ± 1.6	47.0 ± 1.6	0.086
Bust (cm)	49.7 ± 2.9	49.6 ± 2.6	0.702
LFA Z-scores	0.51 ± 1.1	0.17 ± 1.04	0.006
WFA Z-scores	0.6 ± 1.12	0.48 ± 0.89	0.305
WFL Z-scores	0.45 ± 1.24	0.52 ± 0.96	0.595
HFA Z-scores	0.07 ± 1.1	−0.17 ± 1.19	0.066
Fingertip TSH, mIU/L	1.2 (0.8, 1.7)	1.8 (1.4, 2.3)	<0.001
UIC, µg/L	230 (130, 366)	241 (127, 366)	0.864

Data were expressed as Mean ± SD or Median (P_{25}, P_{75}).
TSH, thyroid stimulating hormone; LFA, length-for-age; WFA, weight-for-age; WFL, weight-for-length; HFA, head-for-age; UIC, urinary iodine concentration.

at birth. A Britain study showed no difference in infantile birth weight and length with various UIC levels during pregnancy [22], even in infants whose mothers were diagnosed with subclinical hypothyroidism or hypothyroidism [18,23]. Similar results were found in our study. While in other studies, for example, in Spain [24], a mildly iodine deficient country, compared with infants with maternal UIC <50µg/L, infantile weight was 189g heavier when their mothers' UIC was within 100-150µg/L. Another study conducted in Wuhan, China, reported that when pregnant women had a UI/Creatinine higher than 500µg/g, their infantile weight birth weight was lighter than those infants with sufficient iodine nutrition (2833 vs 3007g) [25]. Serve iodine deficiency can result in cretinism, a series of irreversible and adverse outcomes of infantile development and growth. Restricted physical growth, as the most obvious symptom of cretinism, affects the entire life cycle of infants [26]. At 18-24 months after delivery, significance was only found in infantile HFA Z-scores among different maternal UIC levels during pregnancy. Only when the maternal UIC was within 100-149µg/L during pregnancy, the HFA Z-scores in infants was above zero, which may impact infantile intelligence, because the head circumference of infants was reported to be related to the distant brain development.

Congenital hypothyroidism can cause delayed psychological and physical development of infants, as well as children. No infants at birth were diagnosed as congenital hypothyroidism in our study due to the iodine nutrition in these areas being a mild-to-moderate deficiency, it's not iodine deficient enough during pregnancy to lead to congenital hypothyroidism in their infants. LFA Z-scores in infants with heel-blood TSH <4.0mIU/L were higher than that with heel-blood TSH ≥4.0mIU/L. Neonatal TSH was reported to be positively related to maternal TSH during pregnancy [27], which correlated with their iodine nutrition. What's more, higher neonatal TSH is followed with high TSH in children at 18-24 months, while this effects on their distant development is still uncertain. So more and deep studies are needed to confirm the influence of mild-to-moderate iodine deficiency during pregnancy on themselves and their infantile health.

In conclusion, even if the iodine nutrition during pregnancy was mildly deficient, it may affect their infantile physical development, especially the head circumference, which is related to brain development distantly. Further studies need to be conducted to clarify the effects of mild iodine deficiency during pregnancy on their infants. Surveillance should be continued on pregnant women all around the country.

There are limitations to our study. Firstly, our study only analyzed the effect of iodine-related factors during pregnancy, but other micronutrients were not included. Second, pregnant women and neonates recruited in this study were free of thyroid disease, which may lead to the neglect of some pregnant women who are susceptible to thyroid disease.

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AUTHOR CONTRIBUTIONS

Wanqi Zhang conceived the study. Wen Wu, Yanting Chen, Wenxing Guo, Qi Jin, Naifan Zhang, Kexin Zhang, Ying Yang, and Ziyun Pan participated in this study and collected data. Ziyun Pan was responsible for the analysis of urinary and blood samples and quality control. Wen Wu, Yanting Chen, Wenxing Guo, Qi Jin, Naifan Zhang, Kexin Zhang and Ying Yang analyzed the data, wrote and reviewed the paper. Wanqi Zhang drafted the paper, all authors contributed to and approved the final draft of the manuscript.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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