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Salivary iodine concentrations can estimate iodine intake and diagnose abnormal thyroid function: a cross-sectional study in pregnant and lactating women in iodine-deficient areas

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Abstract

Salivary iodine concentrations (SIC) and urinary iodine concentrations are correlated. This study aimed to verify the use of SIC as a biomarker for estimating iodine intake in pregnant and lactating women and to diagnose abnormal thyroid function. A cross-sectional study was conducted in northern Xinjiang, China. Participants provided venous blood, random urine, saliva and milk samples. A total of 607 pregnant and 171 lactating women volunteered to participate in the study. The average daily iodine intake was calculated for each participant. Pregnant women were divided according to trimester. The median daily iodine intake was 436·41 μg/d in the first trimester, 425·83 μg/d in the second trimester and 430·56 μg/d in the third trimester. The average daily iodine intake in lactating women was 416·16 μg/d. Different indicators were used to diagnose excessive iodine intake (> 500 μg/d). Among pregnant women, SIC had an AUC of 0·62 ($P < 0·01$), sensitivity of 51·75 % and specificity of 65 %. Among lactating women, SIC had an AUC of 0·63 ($P = 0·03$), sensitivity of 43·52 % and specificity of 85 %. SIC was an effective biomarker for diagnosing abnormal thyroid function ($P = 0·03$). In conclusion, this study demonstrated that SIC is a reliable biomarker for evaluating both iodine nutrition status and abnormal thyroid function in pregnant and lactating women.

Keywords: **Salivary Iodine Concentrations: Pregnant women: Lactating Women: Individual iodine status: Thyroid function**

Iodine is an essential trace element in the human body that plays a vital role in the neurodevelopment during fetal development and early childhood[1,2]. Iodine deficiency during pregnancy and infancy may impair the growth and neurodevelopment of the infant and increase infant mortality[3]. The cerebral cortex of the fetus depends on the mother's thyroxine, which produces triiodothyronine to bind nuclear receptors and exert biological effects[4]. A study conducted in Sicily, Italy, found that even mild iodine deficiency during pregnancy can have long-term adverse effects on fetal nerves and cognition, and even if there is subsequent adequate iodine intake during childhood, the effect cannot be improved[5]. Malnutrition during pregnancy is directly associated with goitre and thyroid dysfunction[6]. Similarly, iodine nutrition in breast-feeding women has received attention, because breastmilk is the primary nutrient for infants[7,8]. Therefore, it is necessary to understand iodine nutrition in pregnant and lactating women and take effective and targeted measures to prevent iodine deficiency.

In 2007, the WHO, UNICEF and International Council for the Control of Iodine Deficiency Diseases issued guidelines for reliably measuring iodine deficiency disorders[9]. Four indicators, including the median urinary iodine concentration (MUIC), thyroid swelling rate, thyroid-stimulating hormone (TSH) level and thyroglobulin (Tg) level, have been recommended as indicators of iodine deficiency disorders. However, the MUIC represents only the iodine nutritional indicator of the population and does not reflect an individual's iodine nutritional status. During pregnancy, the thyroid volume in iodine-sufficient

Abbreviations: BMIC, breast milk iodine concentration; Cr, creatinine; FT3, free triiodothyronine; FT4, free thyroxine; MUIC, median urinary iodine concentration; SIC, salivary iodine concentration; StI, serum total iodine concentration; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration.

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countries increases by 10 %, whereas that in iodine-deficient areas increases by 20 % to 40 %[6]. Studies have found that thyroid volume in pregnant women in iodine-sufficient areas is mainly related to genetics and not to other factors[10]. TSH is not a sensitive biomarker for iodine deficiency or excess iodine and its value in determining mild iodine deficiency or excess iodine is uncertain[11]. Tg is an indicator of sensitivity to low or high iodine intake[11,12]. However, the laboratory testing costs for TSH and Tg are high; special laboratories and equipment are required and the subsequent costs are relatively high. Therefore, it is particularly important to select appropriate indicators for evaluating the nutritional status of iodine.

Pregnancy and lactation are special periods because both the growth and development of fetuses and babies require nutrients from their mothers. As an important element in regulating metabolism and synthesising thyroid hormones, iodine plays an important role in the development of fetuses and babies before the age of 2 years. Our research aimed to identify economical, non-invasive and easily accessible biomarkers of individual iodine nutrition to provide clinical guidance for pregnant and lactating women.

Materials and methods

Population and study design

We conducted a cross-sectional study of pregnant and lactating women in northern Xinjiang. This study aimed to identify the best indicators for evaluating iodine nutrition at an individual level. We collected data on the iodine intake, serum total iodine concentration (StI), SIC, UIC, urine creatinine ratio (UIC/Cr), breastmilk iodine concentration (BMIC), thyroid function indicators and thyroid volume. Data were also recorded on socio-economic characteristics, pre-pregnancy BMI, gestational week, number of pregnancies and number of abortions.

Our study population included pregnant and lactating women from the northern part of Xinjiang Uyghur Autonomous Region. The southern part of the region had implemented oral lipiodol pills (twice a year, 100 mg/pill), which would have affected the calculation of iodine intake. Therefore, this region was excluded from analysis. This study included pregnant and lactating women from four counties in the Yili region of northern Xinjiang. Forty pregnant and twenty lactating women participated in the study after providing voluntary informed consent. The researcher informed each participant of their test results.

In this study, the rate of excess iodine intake (iodine intake > 500 μg/l) among pregnant women in northern Xinjiang in 2023 in the 'Iodine Deficiency Disease Surveillance' of the whole Xinjiang was 41·52 % as the prevalence of excess iodine intake, and the sample size of the cross-sectional survey was calculated using the formula: When $\alpha = 0{\cdot}05$ and the permissible error $d = 0{\cdot}1P$, then $n\ 400 \times (1-P)/P$. The sample size, n, for the population of pregnant women in the northern border region was calculated to be approximately 564.

Between April and August 2023, 607 pregnant and 171 lactating women were included in the study. The exclusion criteria were as follows: (1) a history of smoking or alcohol abuse; (2) patients who had used iodine-containing lotions in the previous 3 d, taken Huasu amiodarone hydrochloride tablets, or had recently undergone angiography and (3) occupational exposure to iodine (such as medical or personnel use of iodine disinfectants and iodine contrast agents). Our questionnaire consisted of two parts with independent questionnaires: (1) socio-economic characteristics and (2) a 3-day 24-hour dietary recall. The flow chart is shown in Fig. 1. This study was conducted in accordance with the guidelines of the Declaration of Helsinki. All procedures involving human subjects were approved by the Ethics Committee of the Center for Disease Control and Prevention of the Xinjiang Uygur Autonomous Region (number: 2021-07). Written informed consent was obtained from all participants.

Iodine intake survey and calculation

Before starting the survey, our researchers visited the survey area to collect data on foods eaten with high frequency by pregnant and lactating women and the eating habits of the local residents to determine the food's iodine content. The high-frequency foods included eleven major food categories: staple foods, beans and their products, livestock and poultry meat, eggs, milk and their products, seafood, vegetables, fruits and dried fruits, snacks, condiments and salt. The dietary guidelines of Wang[13] were then used with other dietary maps for 3 d. A retrospective dietary survey was conducted, and the data were collated and analysed. Dietary iodine intake comes mainly from food, drinking water and iodised salt and was calculated using the following formula:

$$\text{Dietary iodine intake} = \Sigma\,(\text{intake of various types of food} \times \text{iodine concentration of each food type} + \text{drinking water volume} \times \text{water iodine concentration} + \text{salt intake} \times \text{salt iodine concentration} \times [1 - 20\%]).$$

The 20 % was to make allowance for the cooking loss rate of iodised salt defined by WHO. The drinking water iodine concentration data were obtained from the 2017 Xinjiang Water Iodine Concentration Survey Project, and the edible salt iodine concentration data were obtained from the Xinjiang Iodine Deficiency Area Disease Monitoring Project in 2023.

Food, blood, saliva, breastmilk and urine sample collections and laboratory measurement methods

Food sample collection included unprocessed foods such as vegetables, fruits, nuts, meat, dairy products and snacks. Unprocessed flour and edible oil were collected in sealed bags and transported to the laboratory to determine the iodine concentration. Fasting venous blood samples (5 ml) were collected from each participant. The blood sample was allowed to stand upright for 15 min and then centrifuged at 3000 rpm. After centrifugation, the serum was divided into two 1·5 ml centrifuge tubes (Axygen brand). One part was used to determine the total serum iodine concentration, and the other was used to determine thyroid function. Before saliva collection,

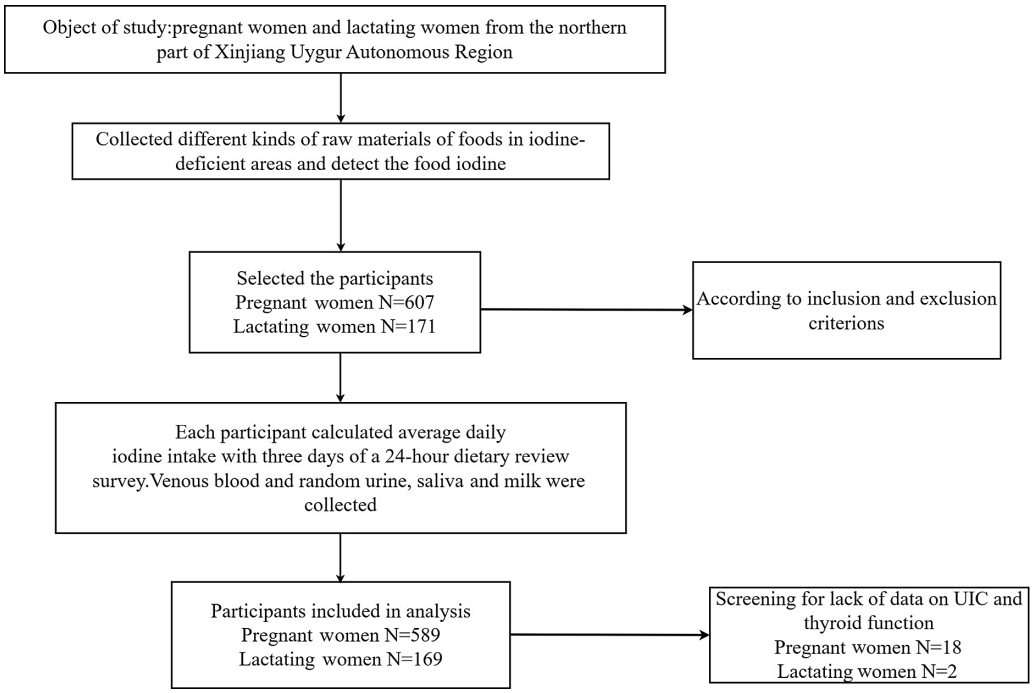

Fig. 1. Flow chart. Participant flow charts.

the participants were asked to rinse their mouths with distilled water. Five minutes after rinsing, the subjects were asked to spit their saliva into a 5 ml sterile plastic tube and seal it. Before milk collection, lactating women were asked to rinse their nipples with distilled water and then squeeze the milk into a 5 ml sterile plastic tube that was then sealed for storage. For the collection of urine, pregnant and breast-feeding women were asked to collect a single dose of urine in the morning before the ultrasound scan and were asked not to eat or drink before collecting the urine. Each participant was given a sterile urine cup and a 5 ml sterile sealed plastic tube. Participants were asked to collect the middle part of the random urine sample into the urine cup and then transfer it to a 5 ml sterile sealed plastic tube. Serum, saliva, breastmilk and urine were transported to the laboratory under cold-chain conditions for measurement. The cold-chain temperature was monitored during this process and was maintained at 2–5°C.

The iodine concentration in food was measured according to the national standard method: *National Standard of the People's Republic of China – National Standard for Food Safety Determination of Iodine in Food Determination of Iodine in Foodstuffs (National Standard No. GB5009·267–2020) Inductively Coupled Plasma Mass Spectrometry (ICP-MS)*. This method was also used to determine serum, breastmilk and SIC. The UIC was determined in accordance with the *Health Industry Standard of the People's Republic of China – Determination of Iodine in Urine Part 2 (WS/T107·2–2016): Electro-inductive Coupled Isotope Mass Spectrometry (ICP-MS)*. The urine creatinine (Cr) concentration was determined in accordance with the People's Republic of China health industry standard 'urine creatinine spectrophotometry photometric method'. A five-item checklist was used to determine thyroid function. A Roche E411 electrochemiluminescence immunoassay analyser was used to measure the levels of free triiodothyronine (FT3), free thyroxine (FT4), TSH, thyroglobulin antibody and thyroid peroxidase antibody (TPOAb).

Standards used and variable definitions

Pregnancy was classified according to trimester, as follows: first trimester, 0–13 weeks; second trimester, 14–27 weeks and third trimester, 28–40 weeks. The recommended daily nutrient intake for iodine intake by pregnant and lactating women and the daily intake that should not be exceeded were considered. The WHO standard was adopted. Iodine intake of less than 250 μg/d was defined as insufficient iodine intake, whereas iodine intake of more than 500 μg/d was defined as excess iodine intake[14]. The pre-pregnancy BMI classification standard adopted by the Chinese adult standard in 2007 classified a BMI between 18·5 and 23·9 kg/m^2 as normal, less than 18·5 kg/m^2 as underweight, between 24 and 27·9 kg/m^2 as overweight, and 28 kg/m^2 or more as obese[15]. The WHO, UNICEF and International Council for the Control of Iodine Deficiency Diseases ICCIDD have evaluated the iodine intake categories in pregnant women. An MUIC < 150 μg/l was classified as insufficient iodine intake; An MUIC between 150 and 250 μg/l was classified as adequate iodine intake and a MUIC between 250 and 500 μg/l was classified as more than adequate. An MUIC > 500 μg/l meant that no added health benefit could be expected. The standard for evaluating iodine intake by lactating women was an MUIC < 100 μg/l was classified as insufficient iodine intake. An MUIC > 100 μg/l was classified as adequate iodine intake[9]. The evaluation criteria for thyroid hormones and autoantibodies were based on the guidelines for diagnosing and treating thyroid

Table 1. Diagnostic criteria for thyroid diseases

Thyroid disease	Diagnostic criteria
Hypothyroxinemia	FT4 decreases, TSH is within the normal range
Hypothyroidism	TSH increases, FT4 decreases
Subclinical hypothyroidism	TSH is elevated, FT4 is within the normal range, and there are no obvious clinical symptoms
Hyperthyroidism	TSH decreased, FT4 increased or early FT3 single item increased
Subclinical hyperthyroidism	TSH decreased, FT3 and FT4 were within the normal range, no obvious clinical symptoms

TSH, thyroid-stimulating hormone.

diseases during pregnancy and the postpartum period[16]. The reference range for normal thyroid function in pregnant women was established using the Roche electrochemiluminescence immunoassay. The standard established by the commonly used instrument kits was as follows: The reference range of FT3 was 3·1–6·8 pmol/l. The reference ranges of TSH by trimester were 0·09–4·52 mU/l in the first trimester, 0·45–4·32 mU/l in the second trimester and 0·30–4·98 mU/l in the third trimester. The reference range of FT4 was 13·15–20·78 pmol/l in the first trimester, 9·77–18·89 pmol/l in the second trimester and 9·04–15·22 pmol/l in the third trimester. The reference range of thyroglobulin antibody was 0 – 115 IU/ml. The reference range of TPOAb was 0–34 IU/ml. The criteria for diagnosing thyroid disease are listed in Table 1.

Statistical analysis

The Kolmogorov–Smirnov method was used to verify the normality of the data distribution. Age, gestational week, thyroid volume, FT3, FT4, pre-pregnancy BMI, MUIC, UIC/Cr, StI, SIC, TSH, TgAb and TPOAb were all non-normally distributed data and were therefore reported as medians and interquartile ranges. Medcalc 20·010 software was used to draw receiver operating characteristic (ROC) curves to test SIC, BMIC, UIC, StI, UIC/Cr and other indicators for diagnosing excessive iodine intake, and abnormal thyroid function. The Spearman correlation coefficient was used to analyse the relationships between SIC and height, weight, BMI, gestational age, parity, UIC and UIC/Cr. The relationship between SIC and age, BMI, UIC, UIC/Cr, thyroid volume and thyroid function was explored using quantile regression, with $\alpha = 0{\cdot}05$ as the threshold for statistical significance. The statistical analysis and plotting of the quantile regression graph were performed using R version 4.03 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

The socio-economic characteristics of the study groups

Of the pregnant participants in this study, 17 % were in their first trimester, and 42·2 % were in their second and 40·9 % were in their third trimester, respectively. The median age was 28 years, and the 25–35-year age group was the largest age group. The mean weight of the women before pregnancy was 57–58 kg, and the mean weight of the lactating women was 63·5 kg. Most participants had a BMI in the normal range (between 18·5 and 23·9 kg/m^2). In the lactating women, 39·8 % were overweight and 12·3 % were obese, which was higher than the pre-pregnancy BMI of the pregnant women. The proportion of first birth or first pregnancy was lower than that of previously pregnant women. Among women in the second trimester, 16·2 % were experiencing their first pregnancy or birth, whereas 26·0 % had a previous pregnancy. In the lactating women, the proportion of first delivery or first pregnancy was 46·8 %. The annual income was relatively concentrated in the range of 20 000–30 000 CNY. The level of education was mainly at the junior high school level. The number of pregnant women who had left their jobs was 52·9 %, whereas the proportion of lactating women who had left their jobs was 43·3 %. The proportion of women who had been exposed to second-hand smoke was 18·7 % in lactating women and 9·4 % among women in the second trimester. All pregnant and lactating women consumed iodised salt, and none consumed nutritional iodine supplements (Table 2).

The SIC in pregnant women was lowest in the first trimester, with a median concentration of 128·10 μg/l. The SIC in pregnant women in the third trimester was higher, with a median concentration of 144·19 μg/l. The median concentration of SIC in lactating women was 131·22 μg/l (Fig. 2). The median UIC of pregnant women in the first trimester was higher than 207·21 μg/l, and the median UIC of lactating women (144·80 μg/l) was lower than that of pregnant women. The median serum total iodine concentration in lactating women was 64·21 μg/l lower than that of the pregnant women. The median UIC and UIC to creatinine (Cr) ratio showed the same trend as that of the median UIC. The UIC/Cr ratio was higher in women in the first trimester and lowest in lactating women. The mean BMIC of the lactating women was 380·26 μg/l. The median dietary iodine intake was over 410 μg/d (Table 2).

Comparison of different indexes in diagnosing excessive iodine intake and abnormal thyroid function

Iodine overdose was investigated using different indicators including UIC, SIC, StI, UIC/Cr and BMIC. If the upper limit of iodine intake was set as 500 μg/d, the cutoff values of UIC, SIC, StI and UIC/Cr for evaluating excessive iodine intake would be 339·67 μg/l, 131·63 μg/l, 73·62 μg/l and 282·04 μg/l, respectively. The sensitivity and specificity of these measures for diagnosis are shown in Table 3. Among them, the UIC of pregnant women had a higher sensitivity in diagnosing iodine excess but lower specificity. The sensitivity and specificity of SIC for diagnosing iodine overdose were similar, with the highest specificity and maximum area under the ROC curve (AUC) of 0·62 ($P < 0{\cdot}01$). In lactating women, SIC had the highest specificity for diagnosing iodine overdose (85·00 %), and the highest AUC was 0·63 ($P = 0{\cdot}03$). BMIC had the highest sensitivity (82·41 %), but the specificity was low (35·00 %). Similarly, when using different indicators to diagnose abnormal thyroid function in pregnant and lactating women, the highest specificity of the different indicators was SIC, with an AUC of 0·61 and 0·78 in pregnant and lactating women, respectively ($P = 0{\cdot}02$, $< 0{\cdot}01$). Values greater than 148·12 μg/l and 101·73 μg/l were the best cut-off values for

Table 2. Socio-economic characteristics of pregnant and lactation women (numbers and percentages; mean values and standard deviations; median values and interquartile ranges)

Parameter	Pregnant group (*n* 607)						Lactation group (*n* 171)	
	First trimester 0–12 week (*n* 103; 17·0 %)		Second trimester 13–27 week (*n* 256; 42·2 %)		Third trimester ≥ 28 week (*n* 248; 40·8 %)			
	n	%	*n*	%	*n*	%	*n*	%
Age (year)								
Mean	28·5		28·1		24·4		28·6	
SD	0·5		0·3		0·3		0·4	
Age group								
18–< 25	26	4·3 %	72	11·9 %	82	13·5 %	34	19·9 %
25–< 35	65	10·7 %	160	26·4 %	141	23·2 %	161	67·8 %
≥ 35	12	2·0 %	24	4·0 %	25	4·0 %	21	12·3 %
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Weight (kg)	57·3	0·9	58·7	0·7	58·2	0·7	63·5	0·8
Height (cm)	160·4	0·6	161·8	0·5	162·3	0·4	161·4	0·4
BMI (kg/m^2)	22·3	0·3	22·5	0·3	22·1	0·3	24·4	0·3
	n	%	*n*	%	*n*	%	*n*	%
BMI Classes								
Underweight	13	2·1 %	40	6·6 %	45	7·4 %	12	7·0 %
Normal	61	10·1 %	136	22·4 %	136	22·4 %	70	40·9 %
Overweight	26	4·3 %	59	9·7 %	51	8·4 %	68	39·8 %
Obesity	3	0·5 %	21	3·5 %	16	2·6 %	21	12·3 %
Number of births								
Primiparous	48	7·9 %	98	16·2 %	121	19·9 %	80	46·8 %
Multiparous	55	9·1 %	158	26·0 %	127	20·9 %	91	53·2 %
Total year income (CNY)								
< 20 000	18	3·0 %	37	6·1 %	47	7·7 %	39	22·8 %
20 000–30 000	33	5·4 %	105	17·3 %	81	13·3 %	58	33·9 %
30 000–50 000	26	4·3 %	66	10·9 %	67	11·0 %	36	21·1 %
50 000–100 000	17	2·8 %	42	6·9 %	40	6·6 %	25	14·6 %
> 100 000	9	1·5 %	6	1·0 %	13	2·2 %	13	7·6 %
Education level								
Primary school	9	1·5 %	42	6·9 %	47	7·7 %	19	11·1 %
Junior high school	45	7·4 %	89	14·7 %	76	12·5 %	52	30·4 %
High-school	25	4·1 %	65	10·7 %	68	11·2 %	42	24·6 %
College-level	24	4·0 %	60	9·9 %	57	9·4 %	58	33·9 %
Employment								
Yes	50	8·2 %	124	20·5 %	112	18·5 %	97	56·7 %
No	53	8·7 %	132	21·7 %	136	22·4 %	74	43·3 %
Passive smoking								
Yes	27	4·4 %	59	9·4 %	55	9·1 %	32	18·7 %
No	76	12·5 %	199	32·8 %	193	31·8 %	139	81·3 %
Salt intake								
Don't know	0	0·0 %	0	0·0 %	0	0·0 %	0	0·0 %
Non-iodised	0	0·0 %	0	0·0 %	0	0·0 %	0	0·0 %
Iodised	103	17·0 %	256	42·2 %	248	40·8 %	171	100·0 %
Iodine supplement								
Yes	0	0·0 %	0	0·0 %	0	0·0 %	0	0·0 %
No	103	17·0 %	256	42·1 %	248	40·8 %	171	100·0 %
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
SIC (μg/l)	128·10	68·88–233·01	136·93	63·69–226·54	144·19	69·93–263·97	131·22	64·75–211·39
UIC (μg/l)	207·21	119·27–289·82	177·10	105·13–259·91	170·36	104·95–272·51	144·80	85·78–234·33
StL (μg/l)	89·28	68·22–105·05	90·44	69·39–119·60	88·85	65·70–115·66	64·21	47·55–86·81
UIC/Cr (μg/g)	200·34	100·41–324·87	196·89	106·36–313·92	178·82	93·78–290·90	139·40	83·70–267·88
BMIC (μg/l)	–		–		–		380·26	277·64–515·25
Average daily iodine intake (μg/d)	436·41	340·03–498·69	425·83	363·53–486·02	430·56	367·87–489·62	416·16	368·96–471·94

IQR, interquartile range; SIC, salivary iodine concentrations; UIC, urinary iodine concentrations; BMIC, breastmilk iodine concentration.

diagnosing abnormal thyroid function in pregnant and lactating women, respectively. UIC had the highest sensitivity for diagnosing abnormal thyroid function in pregnant women, whereas BMIC had the highest sensitivity for diagnosing abnormal thyroid function in lactating women. However, the specificities of UIC and BMIC were low (Table 3 and Fig. 3).

Quantile regression model of salivary iodine concentrations and related factors

Spearman rank correlation analysis (Table 4) showed that the SIC of the pregnant women was positively correlated with the number of previous deliveries ($\rho = 0{\cdot}0855$, $P = 0{\cdot}04$) and was

Table 3. Comparison of different indexes in diagnosing iodine intake and abnormal thyroid function

			UIC	SIC	StI	UIC/Cr	BMIC
Diagnosing of excess iodine intake	Pregnant women	Sensitivity (%)	88·67	51·75	71·10	73·64	–
		Specificity (%)	22·31	65·89	40·15	40·77	–
		Youden index	0·11	0·18	0·11	0·14	–
		AUC	0·54	0·62	0·53	0·55	–
		P	0·20	< 0·01	0·34	0·14	–
		Associated criterion	339·67	131·63	73·62	282·04	–
	Lactating women	Sensitivity (%)	54·63	43·52	75·93	75·93	82·41
		Specificity (%)	65·00	85·00	45·00	55·00	35·00
		Youden index	0·20	0·29	0·21	0·31	0·17
		AUC	0·58	0·63	0·59	0·63	0·57
		P	0·24	0·03	0·26	0·08	0·32
		Associated criterion	150·53	110·53	83·90	247·64	547·92
Diagnosing of abnormal thyroid function	Pregnant women	Sensitivity (%)	74·33	54·56	70·07	41·35	–
		Specificity (%)	37·04	74·07	14·81	70·37	–
		Youden index	0·11	0·29	0·15	0·12	–
		AUC	0·51	0·61	0·50	0·50	–
		P	0·83	0·02	0·95	0·97	–
		Associated criterion	267·66	148·12	71·37	149·68	–
	Lactating women	Sensitivity (%)	74·59	64·75	70·49	42·62	73·77
		Specificity (%)	66·67	100·00	83·33	83·33	50·00
		Youden index	0·41	0·65	0·54	0·26	0·24
		AUC	0·70	0·78	0·71	0·53	0·51
		P	0·12	< 0·01	0·12	0·75	0·96
		Associated criterion	89·60	101·73	51·51	174·84	508·41

UIC, urinary iodine concentrations; SIC, salivary iodine concentrations; BMIC, breastmilk iodine concentration; AUC, area under the curve.

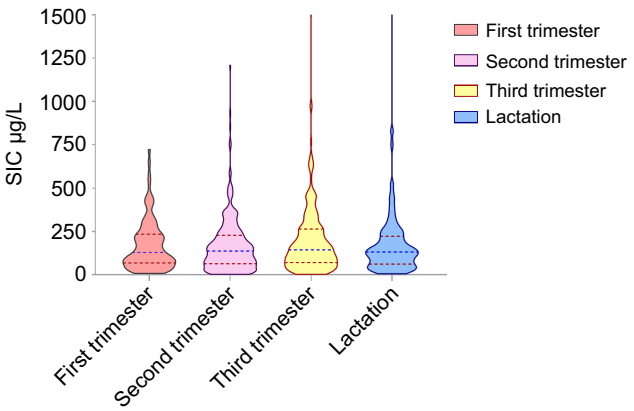

Fig. 2. Violin chart of iodine content in the saliva of pregnant women in different trimesters and the lactation period.

positively correlated with UIC and UIC/Cr (ρ = 0·1869, 0·1367, $P < 0·01$), which were positively correlated with dietary iodine intake and thyroid-related indexes FT3, FT4 and TPOAb. Among the relevant factors for lactating women, only StI was correlated with SIC (ρ = 0·1980, $P = 0·009$) (Table 5).

By incorporating meaningful variables from the Spearman correlation analysis into the quantile regression model, the results for pregnant women showed that the effect of UIC on SIC increased gradually with an increase in UIC below the 35th percentile; however, the effect on SIC changed little after the 35th percentile. The effect of UIC/Cr on SIC below the 35th percentile gradually decreased as the value increased; however, above the 35th percentile, the effect on SIC gradually increased and exceeded the CI of the mean regression. The effect of 3-day dietary iodine intake on salivary iodine was not significantly different from the mean regression. When the FT3 level was low, it was negatively correlated with SIC, but positively correlated after the 30th percentile. With an increase in FT3, the influence on SIC and its regression coefficient gradually increased. When the concentration of FT4 was low, it was positively correlated with SIC and mildly negatively correlated with SIC with an increase in FT4. Below the 50th percentile, the effect of TPOAb on SIC gradually decreased and then increased from a positive correlation to a negative correlation; however, above the 50th percentile and blow the 65th percentile, the effect gradually increased. Above the 65th percentile, the effect on SIC gradually decreased with increasing TPOAb levels. The effect of StI on SIC below the 65th percentile fluctuated slightly; however, above the 65th percentile, the effect on SIC gradually increased with an increase in StI and changed from negative to positive. Quantile regression was not performed for lactating women because of the limited number of relevant variables (Fig. 4).

Discussion

This study shows that salivary iodine can be used as a biomarker to evaluate excess iodine intake and predict thyroid dysfunction in pregnant and lactating women. Moreover, it is more convenient to obtain materials that are easy to operate and detect. Few studies have been conducted on biomarkers for iodine nutrition in pregnant and lactating women. The Netherlands-based Generation R (iodine sufficient) and the Spain-based INMA (mildly-to-moderately iodine-deficient) cohorts used thyroglobulin as a biomarker of iodine status in iodine-sufficient and mildly iodine-deficient pregnant

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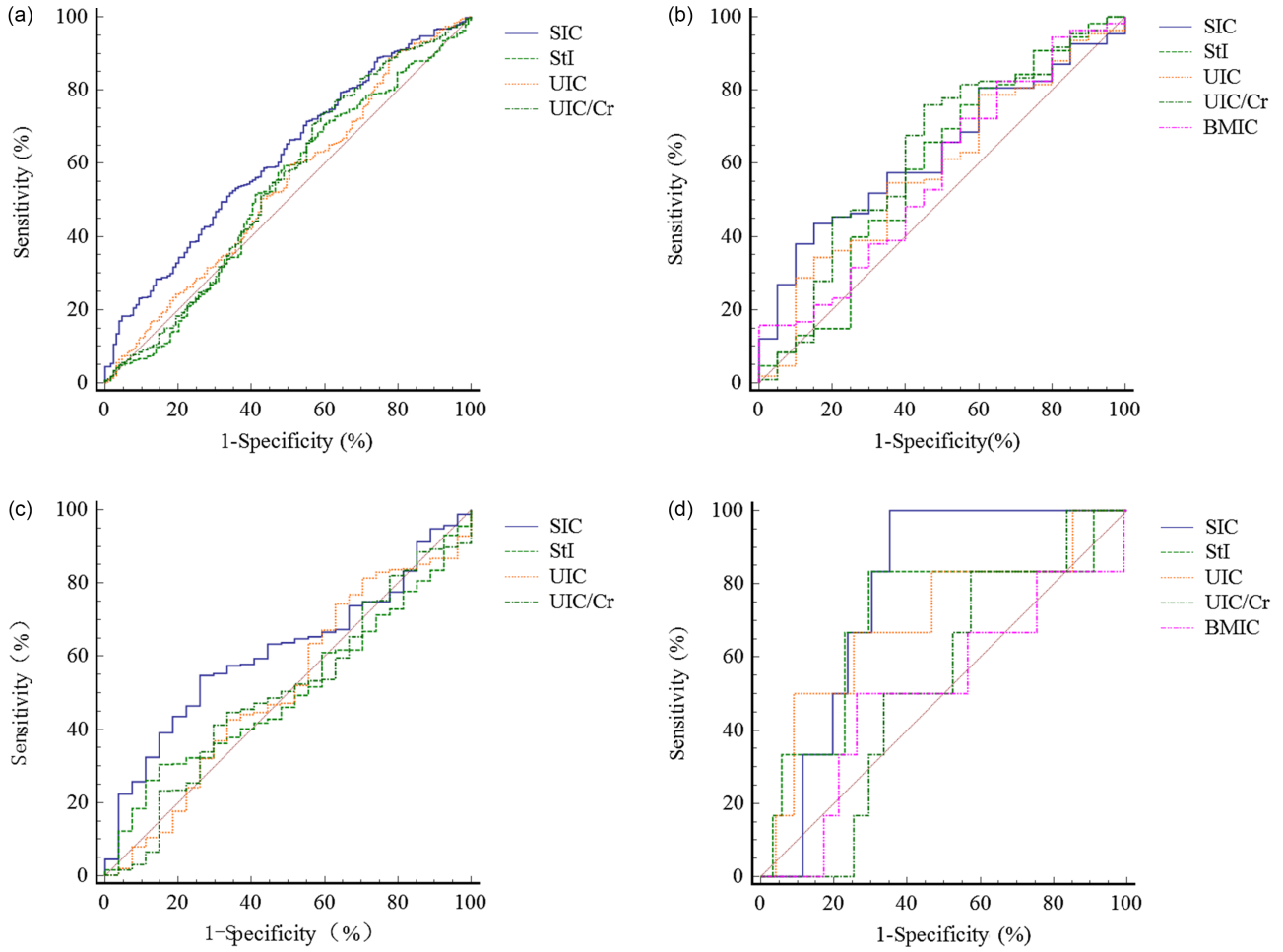

Fig. 3. Receiver operating characteristic (ROC) curve for different indexes in diagnosing excessive iodine intake and abnormal thyroid function (a) ROC curve for diagnosing excessive, (b) ROC curve for diagnosing excessive iodine intake in pregnant women iodine intake in lactating women, (c) ROC curve for diagnosing, (d) ROC curve for diagnosing abnormal thyroid function in pregnant women abnormal thyroid function in lactating women.

women[17]. The results of a cross-sectional survey of lactating women in Taiwan and China suggested that measuring maternal UIC alone may not be sufficient, as BMIC, UIC/Cr, and 24-h UIE were all important biomarkers. Ingestion of dairy products and multivitamins was independently associated with BMIC[18]. In a multicentre Chinese population-based mother and child cohort in Zhejiang, SIC was shown to be a potential biomarker for assessing individual iodine nutrition and thyroid dysfunction in pregnant women[19]. A cross-sectional survey conducted in Tianjin, China, showed that serum iodine levels can be used as an indicator of the nutritional iodine status and thyroid dysfunction[20]. One study, which started in June 2012 in Liaoning Province in an iodine-adequate area in China, found that UI/Cr reflected the 24-hour iodine excretion and circulating iodine levels during pregnancy and postpartum[21]. A cohort study in Zhejiang, China, found thyroglobulin to be a sensitive biomarker of iodine status in mildly and moderately iodine-deficient pregnant women[22].

Currently, UIC in a single random urine sample cannot solve the problem of unbalanced iodine intake caused by dietary habits among different individuals. Researchers need to identify an evaluation index suitable for assessing individual iodine nutrition in the population of pregnant and lactating women[23,24]. The physiological structure and hormonal profile of this population undergo significant alterations during pregnancy[6].

Existing research needs to identify a biomarker suitable for individual iodine nutrition in pregnant and lactating women. A meta-analysis found that, although Tg could be used as an evaluation index for iodine deficiency, there are still limitations in adults and pregnant women. In addition, it was not sensitive to changes in iodine intake[25]. Ji *et al.*[26] found that StI truly reflects iodine nutritional status in pregnant women. However, venous blood extraction is an invasive process that making it less accepted by pregnant women. SIC is an economical, easy-to-detect, and non-invasive biomarker. The salivary and thyroid glands have similar iodine-enriching functions. Dekker *et al.*[27] used SIC to estimate the iodine status of adults in clinical practice and achieved significant results. Guo *et al.*[28] found a good correlation between SIC and UIC and concluded that SIC was

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Table 4. Correlation analysis between SIC of pregnant women and selected anthropometric and iodine status variables

Variable	ρ	*P* value
Age	0·04	0·39
Height	0·01	0·96
Weight	−0·02	0·56
BMI	−0·04	0·31
Gestational week	0·03	0·47
Production times	0·09	0·04
UIC	0·19	< 0·01
UIC/Cr	0·14	< 0·01
StL	−0·07	0·08
Thyroid volume	−0·05	0·25
Thyroid nodule	−0·01	0·97
Dietary iodine intake for 3 d	0·28	< 0·01
FT3	0·12	< 0·01
FT4	0·12	< 0·01
TSH	−0·04	0·31
TPOAb	0·09	0·03
Tg	0·04	0·33

SIC, salivary iodine concentrations; UIC, urinary iodine concentrations; TSH, thyroid-stimulating hormone.

Table 5. Correlation analysis between salivary iodine concentration and selected human indexes and iodine status variables in lactating women

Variable	*r*	*P* value
Age	0·06	0·41
Height	0·06	0·47
Weight	0·01	0·86
BMI	−0·04	0·61
Production times	−0·01	0·90
UIC	0·03	0·68
UIC/Cr	−0·05	0·49
StL	0·20	< 0·01
Thyroid volume	0·04	0·59
Thyroid nodule	0·07	0·34
Dietary iodine intake for 3 d	0·09	0·24
FT3	0·02	0·79
FT4	0·01	0·90
TSH	0·07	0·36
TPOAb	0·09	0·23
Tg	0·09	0·26

UIC, urinary iodine concentrations; TSH, thyroid-stimulating hormone.

useful for diagnosing iodine deficiency and excess. SIC can also be used as an indicator of the nutritional iodine status of individuals and populations. Furthermore, it does not have seasonal changes or diurnal variation[29]. However, if SIC is to be used as a biomarker of iodine excess or iodine deficiency, it needs to be validated in different populations, and appropriate cut-off values for each population should be calculated. Guo *et al.*[28] also found significant reference values for the diagnosis of iodine deficiency with SIC of less than 105 μg/l and for the diagnosis of iodine excess and thyroid nodules with SIC of more than 273 μg/l. We also found that SIC can be used to diagnose abnormal thyroid function in pregnant and lactating women. SIC values greater than 148·12 μg/l and 101·73 μg/l were the best cut-off values in pregnant and lactating women, respectively. Dietary deficiency or iodine (I) excess plays an important role in the oral mucosa and salivary gland physiology. Absorption occurs through the same sodium iodide symporter (NIS) receptor as that in the thyroid, and this receptor is expressed in the salivary glands, breast, stomach and placenta. At the beginning of gastrointestinal circulation, saliva recovers iodine that is not absorbed by the thyroid or peripheral tissues from the blood. Iodine is transported and accumulated by NIS through the membrane of the ductal salivary basolateral (BL) surface of the salivary cells of the ductal epithelium[30]. Gastric salivary clearance and secretion of iodine is an important part of the gastrointestinal iodine cycle, accounting for approximately 23 % of the iodine reservoir in the human body. The salivary and thyroid glands share iodine concentration capacity through sodium iodide homology (NIS) and peroxidase activity[31,32]. A correlation between SIC, UIC and UIC ratio was found in pregnant women. Guo *et al.*[28] found a strong correlation between salivary and urinary iodine[28]. Gulaboglul *et al.*[2] also found a close relationship between salivary and urine iodine. SIC determination should be considered as a non-invasive measurement method if it can replace the use of serum for detecting thyroid dysfunction, especially for screening neonatal thyroid dysfunction. The non-invasive saliva collection method is preferable to the collection of neonatal heel blood to screen for hypothyroidism.

This study has some limitations. First, only individuals from iodine-deficient areas were included. Studies should also be conducted among pregnant and lactating women from iodine-adequate and iodine-excess areas. Second, due to the cross-sectional nature of the survey, we did not continuously collect biological samples from pregnant women during the third trimester. As serial samples were not collected during the first, second and third trimester and during lactation, the sample collection process was not dynamic or continuous. Moreover, we did not collect information on the iodine nutritional status of the pregnant women before pregnancy. As with urine, individual variability in saliva was not considered and corrected for. For example, creatinine levels are measured in to correct for urinary iodine levels, and saliva should be measured for salivary amylase to correct for salivary iodine levels[33]. Lactating women cooperated poorly and could not complete the collection of blood, urine, saliva and milk. Most of the participants cared for their children alone at home. This resulted in a low number of breastfeeding women participating in the survey.

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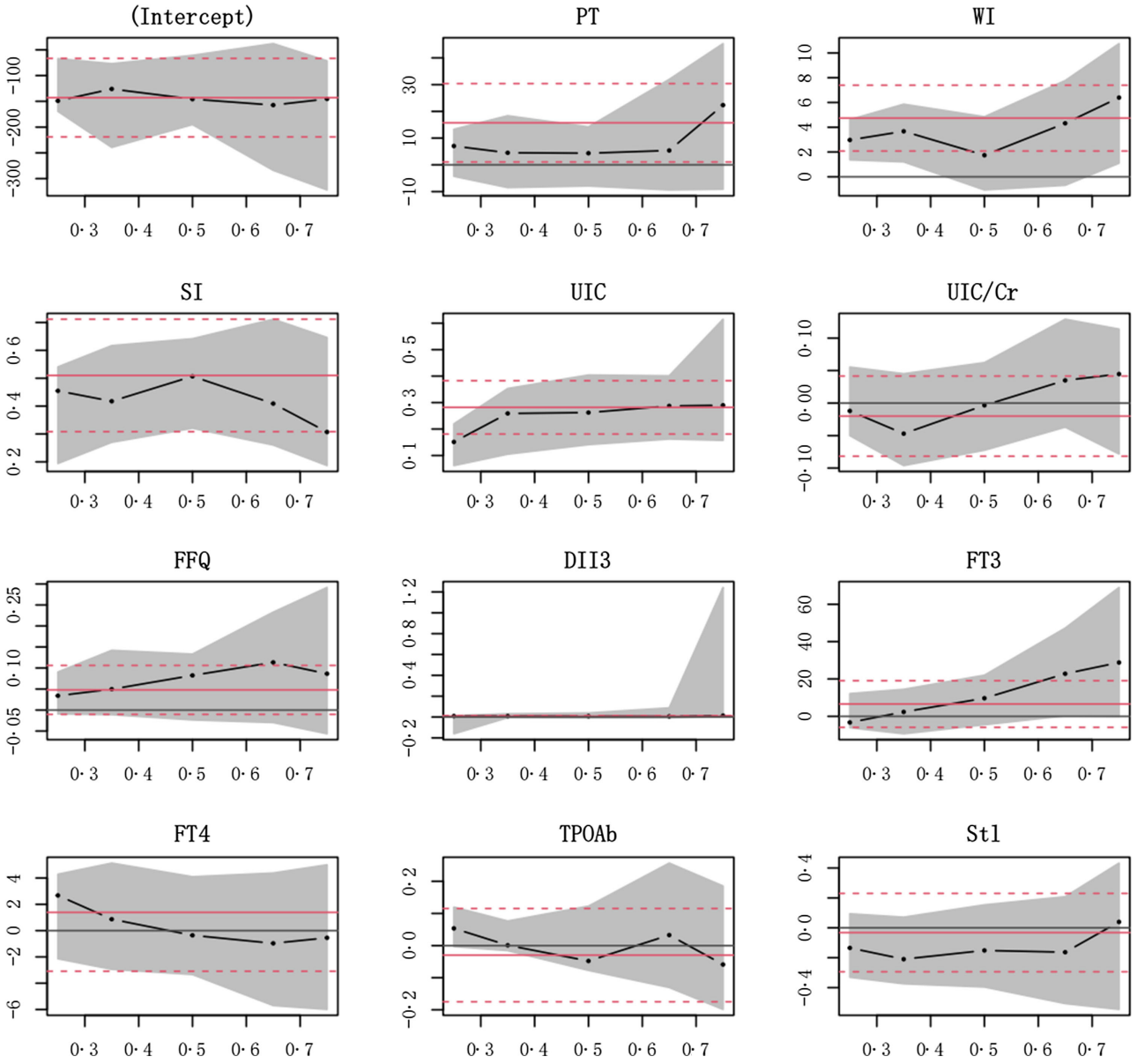

Fig. 4. Quantile regression model for SIC-related factors in pregnant women Spearman correlation was used to analyse the relationships between SIC and height, weight, BMI, gestational week, parity, urine iodine, UIC/Cr, and SIC, Stl were analysed with regression with quantiles if $P < 0{\cdot}05$. SIC, salivary iodine concentration; UIC, urinary iodine concentration; Stl, serum total iodine concentration; UIC/Cr, urine creatinine ratio; BMIC, breast milk iodine concentration; μg/l, microgram/liter; μg/g, microgram/gram; FT4, free thyroxine; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; PT, production times; WI, drinking water iodine concentration; SI, salt iodine concentration; DII3, dietary iodine intake for 3 days – average daily iodine intake.

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The authors declare no conflicts of interest.

The data presented in this study are available on request from the corresponding author. The data are not publicly available because they contain personal information.

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