Original Article

Iodine status of pregnant women in the Chinese plateau area – effects on thyroid function as well as adverse pregnancy and fetal outcomes

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Background and Objectives: This study investigated the iodine status of pregnant women at an average altitude of approximately 2000 meters in Qujing, China. The relationship between iodine and thyroid function in different trimesters as well as adverse pregnancy and fetal outcomes were also investigated. **Methods and Study Design:** A total of 1,025 pregnant women who were admitted to Qujing Affiliated Hospital of Kunming Medical University from January 2019 to August 2021 were included. Urinary iodine concentration (UIC) was detected by colorimetric method, and serum thyroid function was detected by chemiluminescence. Among them, 537 pregnant women were followed up to analyze the association of iodine with adverse pregnancy and fetal outcomes. **Results:** The median UIC was 127 μg/L. Serum triiodothyronine, thyroxine, free triiodothyronine, and free thyroxine were negatively associated with urinary iodine concentration in the first and second trimesters of pregnancy. The proportion of pregnant women testing positive for thyroid peroxidase antibody (TPO-Ab) and the prevalence of thyroid autoimmunity (TAI) increased significantly in more-than-adequate iodine and excess iodine groups. Logistic regression analysis showed maternal iodine was not associated with adverse pregnancy and fetal outcomes. **Conclusions:** Mild iodine deficiency is common among pregnant women in plateau areas of China. The relationship between iodine and thyroid function is significant in the first and second trimesters of pregnancy, especially in those with moderate to severe iodine deficiency. Abnormal iodine level in pregnant women was not significantly associated with adverse pregnancy and fetal outcomes in areas with predominantly mild iodine deficiency.

Key Words: iodine, thyroid function, pregnancy outcomes, fetal outcomes, Qujing

INTRODUCTION

Iodine is an essential trace element and crucial in the production of thyroid hormones, which play a critical role in normal metabolic activities, neurodevelopment and fetal development.[1, 2] Iodine requirements during gestation increase to fulfil both fetal needs and altered maternal thyroid physiology. In healthy pregnant women with adequate iodine intake, these adaptations occur normally and ensure fetal and maternal needs throughout pregnancy. Conversely, if the mother is exposed to insufficient or excessive iodine, this adaptive change may become abnormal, ultimately affecting thyroid function and potentially leading to adverse pregnancy and neonatal outcomes.[3, 4] Thus, both iodine deficiency and iodine overload may be of concern.

Following the implementation of China's universal salt iodization policy, recent surveys in Chongqing, Chengdu,

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Qingdao and other provinces showed that pregnant women showed adequate iodine nutritional status.[5-7] However, iodine status is not only dependent on dietary intake but also affected by the iodine content in the soil. Different altitudes have different effects on iodine nutritional situations and thyroid disease distribution.8 Regions with high altitude and low air humidity makes iodine absorption and storage difficult. This can potentially result in iodine deficiency among residents living in the plateau regions. Nevertheless, dietary practices specific to the plateau regions, including a preference for high-salt diet and preserved foods like ham and pickles, could contribute to higher iodine consumption. Thus, there is a need to further explore the adequacy of iodine in those living in plateau areas. Recent research showed that adults inhabiting the Tibetan plateau in China exhibit a greater prevalence of iodine deficiency compared to individuals residing in lowland areas.[9] Nevertheless, there is a scarcity of studies on the iodine status of pregnant women in plateau regions of China.

Research has demonstrated that in addition to the thyroid gland, the placenta acts as the primary organ for iodine storage.[10] It is hypothesized that the strict control of iodine transport by the placenta is essential to protect the fetus from excessive iodine exposure while simultaneously supporting the production of thyroid hormones. Interestingly, iodine levels can influence the availability of thyroid hormones in the placenta. The optimal levels of these hormones are vital for the proliferation and differentiation of cytotrophoblastic cells, as well as for regulating the invasion of the extravillous trophoblastic layer and maintaining an anti-inflammatory environment within the placenta in cases of maternal thyroid dysfunction.[11, 12] Therefore, any disruptions in the availability of thyroid hormones within the placenta could result in impaired placental function. Several studies have evaluated the relationship between iodine deficiency and adverse pregnancy outcomes, but controversial results were reported.[13, 14] A previous study has reported that iodine deficiency during pregnancy is associated with hypothyroidism, subclinical hypothyroidism (SCH), and thyrotoxemia, which can lead to spontaneous abortion, premature delivery, premature rupture of membranes, and other adverse pregnancy outcomes.[13] Nevertheless, a meta-analysis found that there was no significance was observed between iodine nutrition and pregnancy outcome, including preterm birth, low birth weight, gestational hypertension and preeclampsia, among pregnant women with normal thyroid function.[14] However, the relationship between iodine deficiency and pregnancy outcomes remains inconclusive among pregnant women residing in plateau areas.

To address these important knowledge gaps, our present study aimed to explore the characteristics of iodine status in pregnant women living in plateau areas. The relationship between iodine nutrition status and thyroid function, thyroid autoimmunity, and adverse pregnancy outcomes were also analyzed. These findings will help provide references for the monitoring and intervention of iodine status in pregnant women living in plateau areas.

METHODS

Participants

Considering the seasonal factors, this study included 1,025 pregnant women who were admitted to Qujing Affiliated Hospital of Kunming Medical University from 1st January 2019 to 31st August 2021, to investigate the iodine nutrition status of pregnant women. Inclusion criteria included women with single pregnancy, long-term residence (≥ 5 years) in Qujing, and voluntary participation in our study. Those who previously had thyroid disease (hyperthyroidism, hypothyroidism and thyroid malignancy), taking medications that may affect thyroid function (levothyroxine sodium tablets, methimazole, propylthiouracil, amiodarone, interferon alpha, lithium), had an autoimmune disease (systemic lupus erythematosus, antiphospholipid antibody syndrome, etc.) were excluded. Among them, 625 pregnant women with complete residential address information were selected to explore the difference of iodine nutrition level between urban and rural residents. Also, a total of 936 pregnant women with complete thyroid function measurements, were studied to explore the relationship between iodine status and thyroid function in the first, second and third trimester of pregnancy. 537 pregnant women were followed up for pregnancy outcomes.

Ethics approval

The ethics committee of Qujing Affiliated Hospital of Kunming Medical University, approved the study, approval No. 2020-012 (Section)01. Each participant provided their written informed consent.

Procedures

Information on age, ethnicity, weight, height, time of last menstrual period, number of pregnancies, self-report diseases, morning sickness, taste preference, frequency of high iodine food (such as kelp and seaweed) consumption (500 g per serving), frequency of dairy product consumption (using milk as an example, 250 mL is considered as one serving), family history, and reproductive history were obtained from the questionnaires. Height and weight were measured following a standard procedure with calibrated equipment. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Pregnant women were followed up until delivery, and the mode of delivery, time of delivery, and adverse pregnancy outcomes were recorded.

Thyroid function and urinary iodine tests

Fasting venous blood (5mL) was drawn from subjects early in the morning, and centrifuged at room temperature to separate the serum. Then, thyroid function was measured using a Sorin LIAISON-XL chemiluminescence immunoassay analyzer (Soling Diagnostics, Italy). Thyroid function measurements included levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), total thyroxine (TT4), free triiodothyronine (FT3), total triiodothyronine (TT3), anti-thyroglobulin antibody (TG-Ab) and TPO-Ab.

Fasting mid-stream urine (20 mL) were collected from subjects who had fasted for at least 8 hours early in the morning, and urine iodine concentration was measured by

the colorimetric method using a Qingdao Sankai Medical Technology Co. Ltd. urine iodine analyzer with a certified urinary reference substance to ensure accuracy and an inter-trial coefficient of variation (CV) of <15%. Median urinary iodine concentration was used in this study to assess the iodine status of pregnant women. Iodine status was classified as deficient (≤149 μg/L), adequate (150-249 μg/L), more-than-adequate (250-499 μg/L), and excess (> 500 μg/L).[15]

Definition of thyroid disease during pregnancy

Thyroid diseases include hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, SCH, hypothyroxinemia, autoimmune thyroid diseases. As shown in Supplementary Table 1, thyroid diseases were defined according to the "Guideline on diagnosis and management of thyroid diseases during pregnancy and postpartum (2nd edition)" issued by China in 2019.16 Abnormal thyroid function was defined as the occurrence of one or more thyroid disease during pregnancy, pregnant women serum TPO-Ab ≥ 16 IU/mL and serum TSH > 2.5 mIU/L.

Definition of pregnancy outcomes

Adverse pregnancy and fetal outcomes included gestational diabetes mellitus (GDM), hypertensive disease during pregnancy (HDP), intrahepatic cholestasis of pregnancy (ICP), preterm birth, spontaneous abortion, abnormal amniotic fluid, umbilical cord entanglement, placenta previa, postpartum hemorrhage, fetal distress, fetal macrosomia, fetal growth restriction, neonatal jaundice, and neonatal hypothyroidism.

GDM was defined as fasting glucose ≥ 5.1 mmol/L or 1-hour glucose ≥ 10.0 mmol/L or 2-hour glucose ≥8.5 mmol/L on an oral 75 g glucose tolerance test at 24-28 weeks of gestation.[17] HDP included hypertension during pregnancy, pre-eclampsia, chronic hypertension (any cause diagnosed before 20 weeks' gestation), and chronic hypertension superimposed on pre-eclampsia.[18] ICP was the occurrence of pruritus and elevated serum total bile acids during the second and third trimester of pregnancy, and excludes other possible causes of pruritus and abnormal liver function in pregnant women.[19] Preterm birth was defined as the pregnancy to 28 weeks but less than 37 weeks delivery, not including the pre-eclampsia, placenta previa, fetal growth restriction, and other factors caused by iatrogenic prematurity. Spontaneous abortion was defined as spontaneous abortion before 28 weeks of gestation. Amniotic fluid volume abnormalities include polyhydramnios and oligohydramnios. Polyhydramnios was defined as amniotic fluid volume of more than 2000 mL during pregnancy, on the other hand, amniotic fluid volume of less than 300 mL is called oligohydramnios. Cord entanglement was defined as the umbilical cord surrounding the fetal neck, limbs, or trunk. Placenta previa was defined as the placenta below the fetal presentation and attached to the lower uterine segment after 28 weeks of gestation. Postpartum hemorrhage was defined as blood loss of ≥500 mL for vaginal delivery and ≥1000 mL for cesarean delivery within 24 hours of fetal delivery. Fetal distress was defined as the fetus in the womb of acute or chronic hypoxia, based on the abnormal fetal heart rate, and quickened the amniotic fluid pollution of excrement and urine, or acidosis (fetal scalp blood samples showed that pH< 7.20).[16] Fetal growth restriction (FGR) was defined as the birth weight of less than 2.5 kg of live birth. Fetal macrosomia was defined as fetal weight greater than 4 kg at any gestational week. Neonatal jaundice was defined as jaundice of the skin or other organs caused by the accumulation of bilirubin in the body during birth, and the serum bilirubin of the newborn exceeds 5-7 mg/dL. Neonatal hypothyroidism was defined as TSH concentration greater than 40 mIU/L measured by the filter paper method within 7 days of birth, or serum TSH concentration >20 mIU/L, or the concentration of serum FT4 below and TSH significantly higher than the age-specific reference range (serum TSH > 9 mIU/L, FT4 < 0.6 ng/dL).[16, 20] The incidence of any adverse pregnancy and fetal outcome was defined as presence of GDM, HDP, ICP, premature delivery, abortion, abnormal amniotic fluid, cord entanglement, placenta praevia, postpartum hemorrhage, fetal distress, macrosomia, fetal growth restriction, neonatal jaundice, neonatal hypothyroidism, any of the following. In addition, vitamin D deficiency was defined as serum 25(OH)D < 20 ng/mL.

Statistical analysis

Population characteristics were presented as mean (standard deviation, SD) or median [inter-quartile range (IQR)] for continuous variables and proportions for categorical variables. The differences in population characteristics were compared using ANOVA or chi-square tests, accordingly.

The associations of urinary iodine concentration with thyroid function (FT3, FT4, TSH, TT3 and TT4), were evaluated using Spearman rank correlation and restricted cubic spline analysis. Logistic regression was used to analyze the association of iodine nutrition with adverse pregnancy and fetal outcomes.

A 2-tailed $p<0.05$ was considered to be statistically significant in all analyses. SPSS 25.0 (IBM, Inc., New York, NY, USA) was used for all data analyses.

RESULTS

Study participants and characteristics

The present study included 1,025 pregnant women, with 503 in the first trimester, 378 in the second trimester and 144 in the third trimester. Specific residential addresses of 625 pregnant women were obtained, including 292 from urban areas (Qilin and Jingkai districts), and 333 from other districts. 936 pregnant women had complete thyroid function measurements. A total of 537 pregnant women completed the follow-up of pregnancy outcomes (Figure 1).

Iodine nutritional status of pregnant women in Qujing

The median urinary iodine level of the study population was 127 μg/L. 609 (59.4%) were iodine deficient, 223 (21.8%) iodine adequate, 153 (14.9%) more-than-adequate iodine, and 40 (3.90%) were iodine excess (Table 1). There was no significant differences in maternal age, pre-pregnancy BMI and iodine distribution among the first, second and third trimesters.

Supplementary Table 2 presents data on the dietary habits of pregnant women in relation to their nutritional

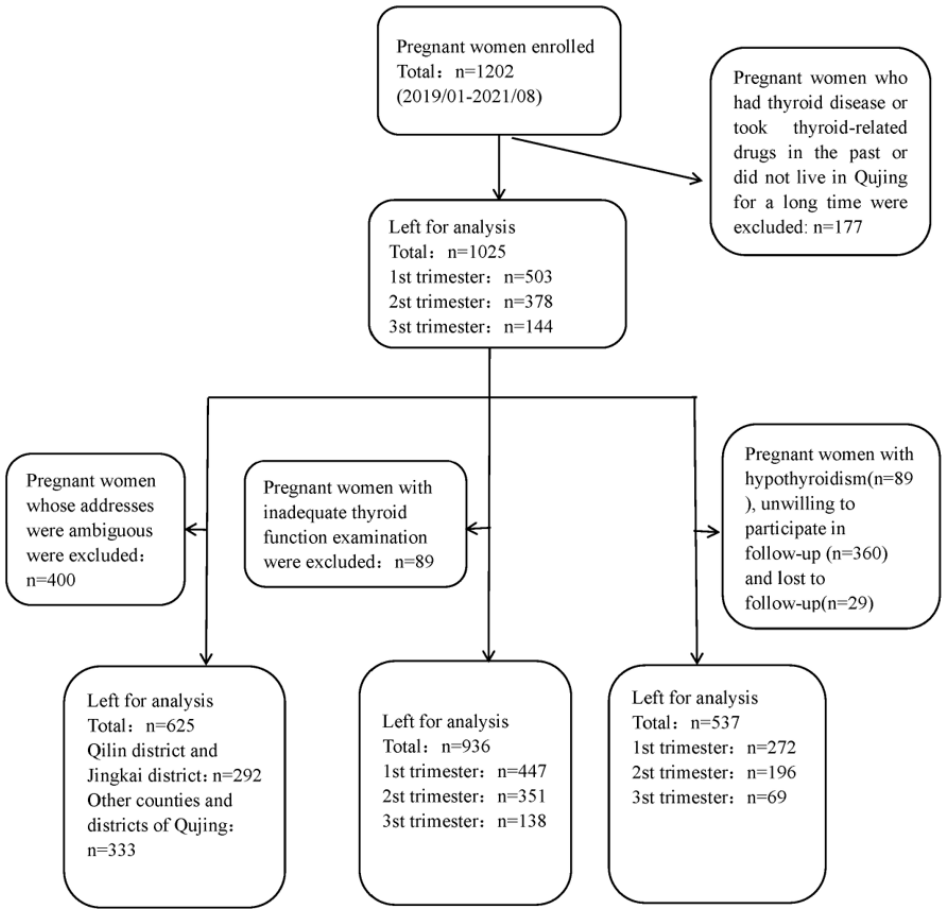

Figure 1. Flow chart of participant

Table 1. Characteristics and iodine nutritional status of pregnant women

Variables	1st trimester	2nd trimester	3rd trimester	Total	*p* value
N	503	378	144	1025	
Age (year)	28.2±4.91	28.5±5.06	28.8±5.07	28.4±4.99	0.320
Gestational week (week)	9±2.75	18.9±3.98	32.3±3.80	15.9±8.71	<0.001
Pre-pregnancy BMI (kg/m^2)	21.8±1.67	21.6±1.65	21.9±1.64	21.7±1.66	0.548
UIC(μg/L)	123 (80.7- 209)	137 (95.3- 209)	124 (92.8- 228)	127 (88.3-210)	0.111
Iodine status [N (%)]					0.490
Deficient	309 (61.4%)	216 (57.1%)	84 (58.3%)	609 (59.4%)	
Adequate	104 (20.7%)	91 (24.1%)	28 (19.4%)	223 (21.8%)	
More-than-adequate	69 (13.7%)	58 (15.3%)	26 (18.1%)	153 (14.9%)	
Excess	21 (4.17%)	13 (3.44%)	6 (4.17%)	40 (3.90%)	

UIC,urinary iodine concentration; BMI, body mass index

iodine status. In terms of taste preference, 77.8% reported consuming a moderately flavourful diet, 9.95% had "heavy taste" and preferred hot and salty flavours, and 12.3% favoured a bland diet. Furthermore, 70.4% of pregnant women never consumed foods high in iodine, such as kelp or seaweed (defined as 500g per serving). On the other hand, 23.4% and 6.15% of the women reported consuming 0.5-1 and 2-3 servings, respectively, of high iodine foods per week. Additionally, 22.6% of pregnant women avoided dairy products (such as milk, 250 mL as one serving), 36.3% consumed 1-3 servings per week, and 41.1% consumed one serving daily. Logistic regression analysis explored the association between pregnant women's dietary habits and iodine deficiency or excess. The findings indicated that pregnant women who consumed one serving of dairy daily had a lower risk of iodine deficiency (OR=0.55, 95% CI: 0.31-0.97). However, after accounting for variables such as ethnicity, primipara status, early pregnancy symptoms, taste preferences, and frequency of high-iodine food consumption, the intake of dairy products was not significantly linked to iodine deficiency. Conversely, pregnant women consuming high-iodine foods 2-3 times per week were more likely to have iodine excess ($OR_{adjusted}$=5.22, 95% CI: 1.52-17.89). No significant correlation was found between dietary taste preference and iodine status in the study population (Supplementary Table 3).

Iodine distribution in urban and non-urban pregnant women

Residential addresses of 625 pregnant women were obtained, including 292 from urban areas (Qilin and Jingkai

districts), and 333 from other districts. No significant difference was observed in maternal age, gestational age, pre-pregnancy BMI, serum 25(OH)D level, median urinary iodine level and distribution of urinary iodine between urban and non-urban pregnant women (Supplementary Table 4).

Urinary iodine concentration and thyroid function during pregnancy

A total of 936 pregnant women had complete thyroid function measurements, including 447 in the first trimester, 351 in the second trimester, and 138 in the third trimester. The median urinary iodine concentration of the 936 pregnant women was 126 μg/L (Table 2). Serum TT3, TT4, FT3 and FT4 levels decreased significantly as pregnancy progressed (Table 2). Participants in the third trimester were more likely to suffer from hyperthyroidism, and had higher 25(OH)D levels. However, no significant difference was found among the three groups in the percentage of TG-Ab positive, TPO-Ab positive, subclinical hypothyroidism, hypothyroidism, subclinical hyperthyroidism, hypothyroxinemia, autoimmune thyroid diseases.

Urinary iodine concentration and thyroid function

Throughout the whole pregnancy, the urinary iodine concentration of pregnant women was negatively correlated with TT3, TT4, FT3 and FT4 (all $p < 0.001$), and positively correlated with TSH (r=0.132, $p < 0.001$). There was no significant association between urinary iodine concentration and TG-Ab, TPO-Ab and serum 25 (OH) D levels. Serum TSH was negatively associated with FT3, FT4, TT3, TT4 and serum 25 (OH) D levels, and positively associated with TG-Ab and TPO-Ab levels (all $p < 0.001$) (Supplementary Table 5).

Specifically, in the first trimester, urinary iodine concentration was negatively correlated with TT3, TT4 and FT4 levels (all $p < 0.05$), and positively correlated with TSH levels (r=0.177, $p < 0.001$) among pregnant women. Serum TSH was negative related with serum 25 (OH) D, FT3, FT4, TT3, TT4 (all $p < 0.001$), and positive related with TG-Ab, TPO-Ab and urine iodine concentration ($p < 0.05$) (Supplementary Table 5). In the second trimester, the urinary iodine concentration of pregnant women was negatively correlated with FT3, FT4, TT3, TT4 (all $p < 0.05$). Serum TSH was negatively associated with FT3, FT4, TT3 and serum 25(OH)D ($p < 0.001$), and positively associated with TG-Ab, TPO-Ab ($p > 0.05$). However, there was no significant association between urinary iodine concentration with TSH, TT3, TT4, FT4, FT3, TG-Ab, TPO-Ab, serum 25(OH)D in the third trimester (Supplementary Table 5).

As shown in Figure 2, limited cubic spline regression analysis found that UIC had a nonlinear relationship with TSH ($p_{nonlinear} = 0.048$), but no nonlinear relationship was found with FT3, FT4, TG, TGAb and TPOAb ($p_{nonlinear} > 0.05$).

Changes of thyroid function with different urinary iodine concentrations

Maternal age, gender, pre-pregnancy BMI, ethnicity, and primiparity showed no significant differences across urinary iodine concentration groups. Compared with the adequate iodine group (UIC: 150-249 μg/L), serum TSH decreased in the moderate and severe iodine deficiency groups, and serum FT3, FT4 and TT3 increased in the moderate and severe iodine deficiency group. The positive proportion of TPO-Ab increased significantly in the more-than-adequate and excess iodine groups. The proportion of individuals testing positive for TG-Ab was lowest in the iodine-adequate group and significantly increased at other iodine concentrations (Table 3).

The abnormal rate of thyroid function in the more-than-adequate iodine group was higher than the adequate iodine group. TAI increased in the more-than-adequate and excess iodine groups. TPO-Ab (+) and TSH (2.5mIU/L -

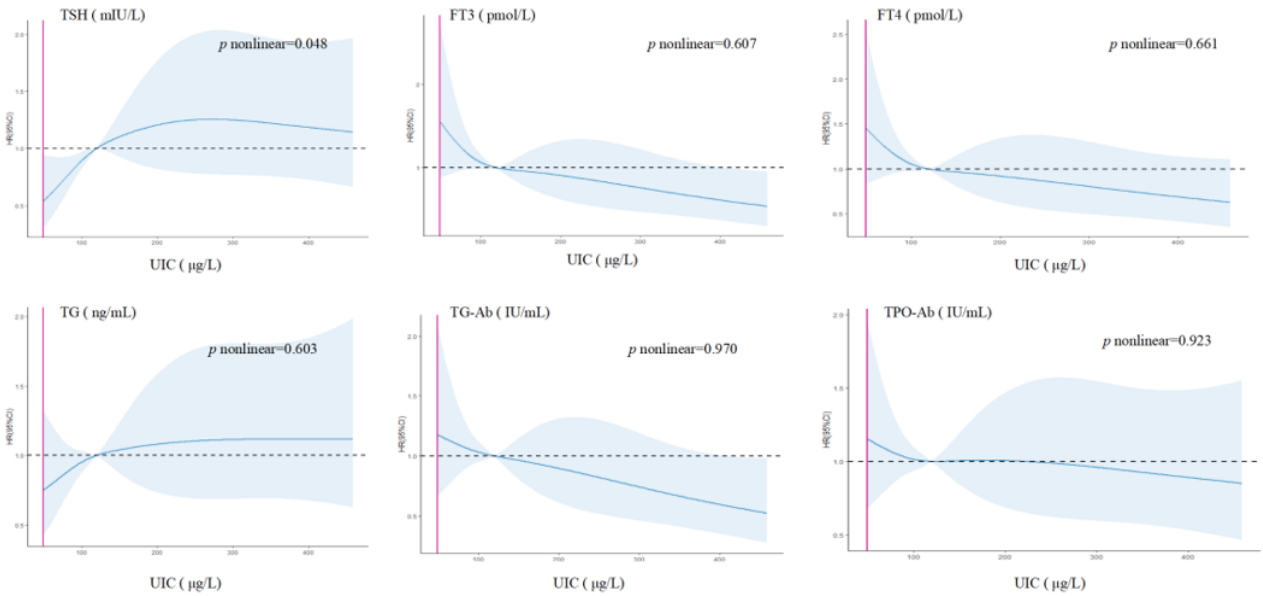

Figure 2. Limited cubic spline analysis of urinary iodine concentration on thyroid function in pregnant women. UIC,urinary iodine concentration; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TG,thyroglobulin; TG-Ab, anti-thyroglobulin antibody; TPO-Ab, anti-thyroid peroxidase antibody

Table 2. Changes in urinary iodine concentration and thyroid function during the three trimesters

Variables	1st trimester (n=447)	2nd trimester (n=351)	3rd trimester (n=138)	*p* value	Total (n=936)
UIC, μg/L	123 (80.5-200)	136(95.20-213)	123 (92.4-211)	0.115	126 (88.2-202)
TSH, mIU/L	2.06 (0.44-3.61)	2.08 (0.96-3.41)	2.27 (1.37-3.61)	0.217	2.09 (0.86-3.49)
FT3, pmol/L	4.03 (3.68-4.64)§	3.71 (3.37-4.09)‡	3.41 (3.14-3.97)‡§	< 0.001*	3.84 (3.40-4.33)
FT4, pmol/L	13.1 (11.4-15.9)§	10.8 (9.67-12.5)‡	10.2 (8.97-11.9)‡§	< 0.001*	11.8 (10.2-14.2)
TT3, nmol/L	1.53 (1.38-1.80)§	1.44 (1.30-1.66)‡	1.40 (1.24-1.63)‡§	< 0.001*	1.49 (1.32-1.72)
TT4, nmol/L	90.3 (76.8-114)§	74.7 (66.8-94.0)‡	73.9 (63.5-99.4)‡	< 0.001*	82.5 (70.0-105.2)
TG, ng/mL	4.55 (0.38-11.4)	4.36 (0.45-9.57)	5.29 (0.21-14.65)	0.419	4.65 (0.41-10.9)
TG-Ab (+), n (%)	126 (28.2%)	89 (25.4%)	39 (28.3%)	0.637	254 (27.1%)
TPO-Ab (+), n (%)	196 (43.9%)	143 (40.7%)	58 (42.0%)	0.675	397 (42.4%)
Thyroid dysfunction, n (%)	272 (60.9%)	217 (61.8%)	91 (65.9%)	0.559	580 (62.0%)
SCH, n (%)	75 (15.7%)	50 (14.3%)	25 (18.1%)	0.481	150 (16.0%)
Hypothyroidism, n (%)	6 (1.26%)	1 (0.28%)	0 (0.00%)	0.227	7 (0.75%)
Hypothyroxinemia, n (%)	6 (1.26%)	1 (0.28%)	0 (0.00%)	0.227	7 (0.75%)
Thyrotoxicosis, n (%)	27 (5.66%)	31 (8.83%)	18 (13.0%)[a]	0.026*	76 (81.2%)
Subclinical hyperthyroidism, n (%)	16 (3.35%)	15 (4.27%)	0 (0.00%)	0.614	31 (3.31%)
TAI, n (%)	196 (43.9%)	143 (40.8%)	58 (42.0%)	0.675	397(42.4%)
TPOAb (+) and TSH, n (%)†	46 (10.3%)	52 (14.8%)	19 (13.8%)	0.141	117 (12.5%)
25(OH)D, ng/mL	17.1±7.00§	18.9±7.41‡	19.6±8.37‡	0.004	18.1±7.38

UIC, urinary iodine concentration; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; TG, thyroglobulin; SCH, subclinical hypothyroidism; TPO-Ab, anti-thyroid peroxidase antibody; TG-Ab, anti-thyroglobulin antibody; TAI, Thyroid autoimmunity.

†2.5mIU/L~upper limit of pregnancy specific reference range.

‡Compared with the 1st trimester.

§Compared with the 2nd trimester.

*$p<0.05$

Table 3. Changes of thyroid function in pregnant women of different urinary iodine concentrations

Variables	UIC, μg/L						*p* value
	<50 (n=42)	50-99 (n=262)	100-149 (n=257)	150-249 (n=203)	250-499 (n=138)	≥500 (n=34)	
Maternal age. years	27.3±4.87	28.2±5.04	28.7±4.92	28.3±4.74	28.9±5.26	29.0±5.64	0.328
BMI, kg/m^2	21.8±1.49	21.6±1.68	21.6±1.71	21.9±1.70	21.9±1.71	22.1±1.26	0.292
Gestational week, weeks	13.9±7.51	15.4±8.55	16.8±9.08	16.0±8.51	17.4±9.73	16.1±8.41	0.189
Ethnic Han, n(%)	36 (85.7%)	240 (91.6%)	238 (92.6%)	188 (92.6%)	129 (93.5%)	34 (100%)	0.137
Primipara, n (%)	20 (47.6%)	114 (43.5%)	125 (48.6%)	92 (45.3%)	63 (45.7%)	11 (32.4%)	0.158
TSH, mIU/L	1.66 (0.09 - 3.02)‡	1.72 (0.34-3.08)‡	2.36 (1.06-3.96)	2.08 (0.92-3.60)	2.31 (1.13-3.87)	2.60 (1.07-2.93)	< 0.001*
FT3, pmol/L	4.16 (3.71-5.50)‡	3.95 (3.44- 4.45)‡	3.85 (3.39-4.36)	3.81 (3.31-4.20)	3.71 (3.33-4.10)	3.77 (3.47-4.27)	0.001*
FT4, pmol/L	13.3(10.7-17.1)‡	12.1 (10.4-15.1)‡	11.8 (10.2-14.0)	11.5 (10.0-13.8)	11.3 (9.52-14.1)	11.3 (9.78-14.0)	0.012*
TT3, nmol/L	1.62 (1.42-2.11)‡	1.51 (1.33-1.80)‡	1.49 (1.34-1.73)	1.46 (1.30-1.68)	1.42 (1.28-1.67)	1.49 (1.38-1.69)	0.005*
TT4, nmol/L	97.1(70.4- 120)	84.1 (71.1-109)	82.6 (69.8-106)	80.7 (69.0-100)	80.8 (66.6-102)	76.7 (67.4-108)	0.079
TPOAb (+), n (%)	13 (31.0%)	61 (23.3%)	49 (19.1%)	52 (25.6%)	68 (49.3%)‡	18 (52.9%)‡	< 0.001*
Tg Ab (+), n (%)	13 (31.0%)‡	61 (23.3%)‡	46 (17.9%)‡	12 (5.91%)	52 (37.7%)‡	17 (50.0%)‡	< 0.001*
Thyroid dysfunction, n (%)	18 (42.9%)	126 (48.1%)	123 (47.9%)	94 (46.3%)	86 (62.3%)‡	19 (55.9%)	0.040*
SCH, n (%)	2 (4.76%)	31 (11.8%)	55 (21.4%)	33 (16.3%)	27 (19.6%)	2 (5.88%)	0.005*
Hypothyroidism, n (%)	0 (0.00%)	3 (1.14%)	2 (0.78%)	2 (0.99%)	0 (0.00%)	0 (0.00%)	-
Hypothyroxinemia, n (%)	0 (0.00%)	2 (0.76%)	3 (1.17%)	1 (0.49%)	1 (0.72%)	0 (0.00%)	-
Thyrotoxicosis, n (%)	4 (9.52%)	33 (12.6%)‡	20 (7.78%)	12 (5.91%)	6 (4.35%)	1 (2.94%)	0.030*
Subclinical hyperthyroidism, n (%)	3 (7.14%)	15 (5.73%)‡	8 (3.11%)	4 (1.97%)	1 (0.72%)	0 (0.00%)	0.035*
TAI, n (%)	13 (31.0%)	61 (23.3%)	49 (19.1%)	52 (25.6%)	68 (49.3%)‡	18 (52.9%)‡	< 0.001*
TPOAb (+) and TSH, n (%)†	3 (7.14%)	16 (6.11%)	9 (3.50%)‡	17 (8.37%)	19 (13.8%)‡	7 (20.6%)	< 0.001*
25(OH), ng/mL	15.3±5.76	18.0±6.88	17.8±7.43	18.2±8.01	18.4±7.45	21.2±7.63	0.133

UIC,urinary iodine concentration; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TT3,total triiodothyronine; TT4, total thyroxine; TG,thyroglobulin; SCH, subclinical hypothyroidism; TPOAb, anti-thyroid peroxidase antibody; TGAb, anti-thyroglobulin antibody; TAI, Thyroid autoimmunity.

†2.5mIU/L: which is the upper limit for pregnancy reference range

‡Compared with urinary iodine concentrations between 150 and 249μg/L

*p<0.05

upper limit of each pregnancy specific reference range) increased in the more-than-adequate iodine group. Hyperthyroidism and subclinical hyperthyroidism increased in the moderate iodine deficiency group. There was no significant difference in the rates of SCH, hypothyroidism and hypothyroxinemia among the iodine groups (Table 3, Figure 3). There was a weak U-shaped relationship between urinary iodine concentration and the rate of thyroid dysfunction and subclinical hypothyroidism in pregnant women. The lowest rate of thyroid dysfunction was observed when the urinary iodine concentration was within 150-249 μg/L. The proportions of TAI, TPO-Ab (+) and TSH (2.5mIU/L -upper limit of each pregnancy specific reference range) increased with the increase of urinary iodine concentration, and were significantly increased in the more-than-adequate group and excess iodine groups.

Association of nutritional iodine with adverse pregnancy and fetal outcomes

There was no significant difference in maternal age, gestational age, mothers aged ≥35 years, gestational week, ethnicity, spontaneous abortion rate, 25(OH)D, hypothyroidism, SCH, hypothyroxinemia, thyrotoxicosis, subclinical hyperthyroidism, TAI, eutocia rate among iodine deficient, adequate, more-than-adequate + excess groups (Table 4). None of the pregnancy outcome, including GDM, HDP, ICP, premature delivery, abortion, abnormal amniotic fluid, umbilical cord around the neck, placenta previa, postpartum hemorrhage, fetal distress, macrosomia, fetal growth restriction, neonatal jaundice, neonatal hypothyroidism and any of the above adverse pregnancy and fetal outcomes, was significant different between the normal and abnormal thyroid function groups (Table 5).

DISCUSSION

Our current study showed that mild iodine deficiency is common among pregnant women in plateau areas of China, and the relationship between iodine and thyroid function is more pronounced in individuals with moderate to severe iodine deficiency. Our study is the first to investigate the relationship between iodine and thyroid function, thyroid autoantibodies, and thyroid disease in pregnant women in Qujing area of Yunnan-Guizhou Plateau, China. However, the study found no correlation between iodine deficiency, more-than-adequate iodine + excess iodine, and adverse pregnancy and fetal outcomes.

Since the implementation of the universal salt iodization policy in China in 1996, iodized salt has become the main source of iodine intake for residents.[21] However, the iodine nutritional status is determined not only by dietary intake but also by the iodine content in the soil. Qujing is located in the plateau region of southwest China, with an average altitude of 2000 meters. In our study, it was found that the median urinary iodine of pregnant women was 126 μg/L (88.2 μg/L - 202 μg/L), and the proportion of iodine deficiency was 59.4%, indicating more than half of pregnant women were mild to moderate iodine deficient. The median urinary iodine concentration observed in this study is comparatively lower than that of pregnant women in plain regions of China, including Shanghai, Jiangsu, and Fujian.[4, 22-24] At the same time, our results showed that there is no significant difference in the proportion of iodine distribution in the three trimesters, and in urban and non-urban areas, indicating that there is no significant regional difference in nutritional iodine status of pregnant women in Qujing. Regardless of the trimester, it is extremely important to timely measure iodine status and provide health education on nutritional iodine for pregnant women. Furthermore, our study demonstrated that the consumption of 1-1.5 kg of high-iodine food per week may result in excess iodine. The iodine content in soil, heightened iodine requirements and excretion, coupled with insufficient knowledge of iodine nutrition in pregnant women, are likely to be the primary factors contributing to aberrations in iodine levels.[7, 9, 25, 26]

The research are controversial on whether there are differences in iodine nutritional status and thyroid function of women during different periods of pregnancy. Our study found that the urinary iodine concentration of pregnant women in the three trimesters were 123 μg/L, 136 μg/L and 123 μg/L, respectively. Also, there was no significant difference in the prevalence of thyroid dysfunction among the three trimesters. This is consistent with the study in Japan and the national surveillance data in Greece.[27, 28] However, some studies have found that the

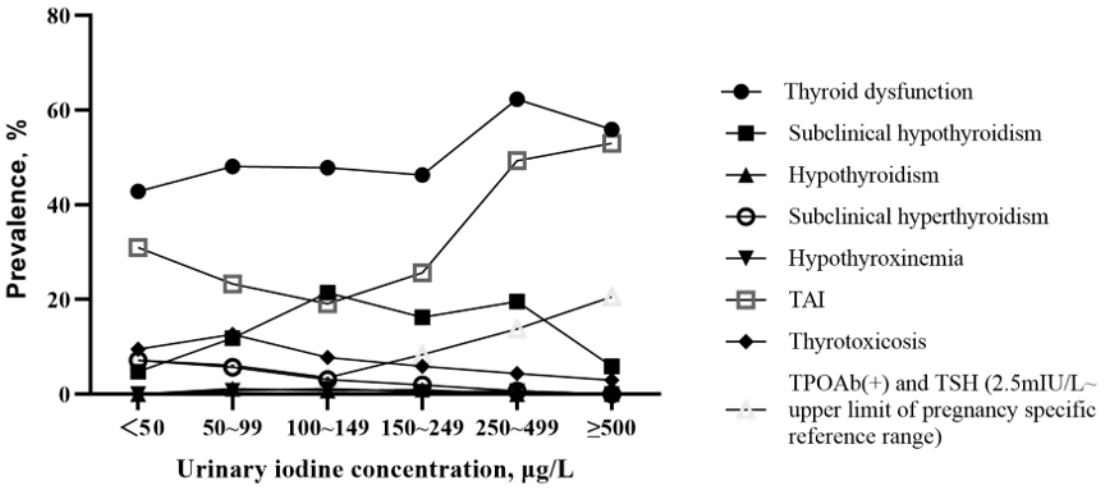

Figure 3. Changes of thyroid diseases in pregnant women under different urinary iodine concentrations

Table 4. Characteristics and thyroid diseases of pregnant under follow up

Variables	Iodine defciency (n=326)	Iodine-adequate (n=115)	Iodine-more-than-adequate + iodine excess (n=96)	Statistics	*p* value
Maternal age , years	28.2±4.69	28.9±4.97	29.3±5.00	2.34	0.098
Age ≥ 35 years, n (%)	34 (10.4%)	16 (13.9%)	17 (17.7%)	3.88	0.144
BMI, kg/m^2	21.5±1.68‡	22.0±1.77†	22.0±1.69†	4.63	0.010*
Gestational week, weeks	15.3±8.34	15.8±8.35	16.2±8.37	0.56	0.572
Ethnic Han, n (%)	300 (92.0%)	106 (92.2%)	91 (94.8%)	0.85	0.652
Primipara, n (%)	151 (46.3%)	52 (45.2%)	41 (42.7%)	0.39	0.822
25(OH)D, ng/mL	17.7±7.21	18.0±7.72	19.2±7.34	1.12	0.326
Vitamin D deficiency, n (%)	215 (66.0%)	72 (62.6%)	52 (54.2%)	4.44	0.109
UIC, μg/L	96.0 (69.3-117)‡	187 (164-216)†	348 (305-473)†‡	408	<0.001*
Hypothyroidism, n(%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	-	-
SCH, n(%)	39 (12.0%)	18 (15.7%)	15 (15.6%)	1.49	0.474
Hypothyroxinemia, n (%)	4 (1.23%)	1 (0.87%)	0 (0.00%)	-	-
Thyrotoxicosis, n (%)	30 (9.20%)‡	1 (0.87%)†	2 (2.08%)†	-	-
Subclinical hyperthyroidism, n (%)	18 (5.52%)	4 (3.48%)	2 (2.08%)	-	-
TAI, n (%)	56 (17.2%)	12 (10.4%)	10 (10.4%)	2.39	0.303
Eutocia, n (%)	199 (61.0%)	61 (53.0%)	54 (56.3%)	2.48	0.290

BMI, Body Mass Index; UIC, urinary iodine concentration; SCH, subclinical hypothyroidism; TAI, Thyroid autoimmunity.
†Compared with the iodine deficiency group.
‡Compared with the iodine - adequate group.
*p<0.05

Table 5. Association of iodine with adverse pregnancy and fetal outcomes[†]

Adverse pregnancy and fetal outcomes and iodine grouping	N	Events (%)	Model 1[‡]		Model 2[§]	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value
The incidence of any adverse pregnancy and fetal outcome						
Adequate	115	25 (21.7%)	1 [Reference]			
Deficiency	326	89 (27.3%)	1.40 (0.84-2.34)	0.196	1.45 (0.86-2.46)	0.164
More-than-adequate + excess	96	21 (21.9%)	1.20 (0.62-2.29)	0.592	1.17 (0.61-2.26)	0.636
HDP						
Adequate	115	2 (1.74%)	1 [Reference]			
Deficiency	326	10 (3.07%)	1.79 (0.37-8.29)	0.458	1.91 (0.41-8.99)	0.413
More-than-adequate + excess	96	1 (1.04%)	0.60 (0.05-6.66)	0.673	0.61 (0.05-6.94)	0.692
Premature delivery						
Adequate	115	4 (3.48%)	1 [Reference]			
Deficiency	326	14 (4.29%)	1.25 (0.40-3.86)	0.704	1.60 (0.50-5.16)	0.430
More-than-adequate + excess	96	3 (3.13%)	0.90 (0.20-4.10)	0.887	0.77 (0.16-3.63)	0.736
Abortion						
Adequate	115	6 (5.22%)	1 [Reference]			
Deficiency	326	11 (3.37%)	0.63 (0.23-1.76)	0.381	0.69 (0.24-1.97)	0.487
More-than-adequate + excess	96	9 (9.38%)	1.88 (0.64-5.48)	0.248	1.99 (0.67-5.91)	0.217
Abnormal amniotic fluid						
Adequate	115	3 (2.61%)	1 [Reference]			
Deficiency	326	14 (4.29%)	1.68 (0.47-5.94)	0.424	1.58 (0.43-5.77)	0.489
More-than-adequate + excess	96	3 (3.13%)	1.20 (0.24-6.11)	0.822	1.15 (0.22-5.93)	0.870
Cord entanglement						
Adequate	115	1 (0.87%)	1 [Reference]			
Deficiency	326	3 (0.92%)	1.06 (0.11-10.3)	0.961	1.16 (0.10-13.0)	0.907
More-than-adequate + excess	96	1 (1.04%)	1.20 (0.07-19.4)	0.898	1.68 (0.10-29.8)	0.724
Placenta previa						
Adequate	115	1 (0.87%)	1 [Reference]			
Deficiency	326	3 (0.92%)	1.06 (0.11-10.3)	0.961	0.74 (0.06-8.60)	0.808
More-than-adequate + excess	96	3 (3.13%)	3.68 (0.38-35.9)	0.263	4.11 (0.39-43.3)	0.240
Fetal distress						
Adequate	115	6 (5.22%)	1 [Reference]			
Deficiency	326	18 (5.52%)	1.06 (0.41-2.74)	0.902	1.09 (0.41-2.89)	0.857
More-than-adequate + excess	96	1 (1.04%)	0.19 (0.02-1.62)	0.129	0.18 (0.02-1.53)	0.116
Macrosomia						
Adequate	115	2 (1.74%)	1 [Reference]			
Deficiency	326	7 (2.15%)	1.24 (0.25-6.06)	0.791	1.36 (0.27-6.75)	0.707
More-than-adequate + excess	96	0 (0.00%)	-	-	-	-

HDP, hypertensive disease during pregnancy.

-: Not statistically analyzed because of small sample size

[†]The incidence of any adverse pregnancy and fetal outcome: presence of gestational diabetes mellitus, HDP, intrahepatic cholestasis of pregnancy, premature delivery, abortion, abnormal amniotic fluid, cord entanglement, placenta praevia, postpartum hemorrhage, fetal distress, macrosomia, fetal growth restriction, neonatal jaundice, neonatal hypothyroidism, any of the following

[‡]Model 1: Univariable logistic regression analysis

[§]Model 2: Adjusted for age≥35 years, primiparity, ethnicity, thyroid disease

*$p<0.05$

urinary iodine concentration of women in different pregnancy periods shows an overall downward trend.[29, 30, 31] This downward trend, to some extent, increases the risk of iodine deficiency in women in the third trimester, but most studies have shown that thyroid dysfunction was still mainly present in the first trimester.[31] However, some studies have found that the urinary iodine concentration of pregnant women increases with the duration of pregnancy. For example, the urinary iodine concentration of women in northern Ireland during the three trimesters was 73 μg/L, 94 μg/L and 117 μg/L, respectively, showing an upward trend.[32] A British study showed that the urinary iodine concentration of women in the first, second and third trimester were 42 μg/L, 52 μg/L and 69 μg/L, respectively, which was also an upward trend.[33] Overall, the urinary iodine concentration of pregnant women in the three trimesters in both iodine adequate and mild deficiency areas did not change significantly, whilst may decline or increase with pregnancy duration in iodine moderate and severe deficiency areas. The iodine reserve of pregnant women in iodine adequate and mild iodine deficiency areas is sufficient, and there is no significant effect on the synthesis of thyroid hormone. Therefore, urinary iodine excretion is similar across all three trimesters, with no significant difference in the rate of thyroid dysfunction. Pregnant women in areas with moderate or severe iodine deficiency have less iodine or thyroid hormone reserve, and most of the iodine intake is used to synthesize thyroid hormone, resulting in reduced urinary iodine excretion during pregnancy. The reason why the urinary iodine concentration of pregnant women increased or decreased with the increase of pregnancy may be that the pregnant women took iodine supplements during different periods of pregnancy. Most people pay attention to the iodine nutritional status of women in early pregnancy, resulting in high urinary iodine concentration. Attention to iodine nutrition declines as pregnancy progresses, leading to a decrease in urinary iodine concentration among pregnant women. However, some studies have shown pregnant women start taking iodine supplements in the second or third trimester, and dietary iodine intake, such as dairy products, increases with the progression of pregnancy, resulting in the increase of urinary iodine concentration in the second and third trimester.[27, 34]

Previous studies only observed the relationship between iodine and thyroid function in the first trimester, and therefore a lack of research on different pregnancy periods or different nutritional iodine levels. This study found that the positive correlation between TSH and urinary iodine concentration occurred in the first trimester. Additionally, a non-linear correlation was revealed by restricted cubic spline regression analysis. The negative correlation between FT3, FT4, TT3, TT4 and urinary iodine concentration occurred in the first and second trimester of pregnancy. In the third trimester, there is no significant correlation between thyroid function and urinary iodine concentration of pregnant women. This is consistent with the findings from a Spanish survey of pregnant women.[34] This study included women with urinary iodine concentrations of 109 μg/L in the first trimester and 172 μg/L in the second trimester, and no association between urinary iodine concentration and TSH was found in women in the first trimester. However, there was a weak positive correlation between urinary iodine concentration and TSH in the second trimester, and there was a weak negative correlation between urinary iodine concentration and FT4, and no correlation with FT3. In another study conducted in Tehran, the urinary iodine concentration of women in the first and second trimesters was not significantly correlated with FT4 and TSH, but only a weak negative correlation was found between urinary iodine concentration and TSH in the third trimester, which may be attributed to the region being iodine-sufficient.[35] The urinary iodine concentrations of pregnant women in the three trimesters were 218 μg/L, 160 μg/L and 145 μg/L, respectively, which were significantly higher than those in this study. Similarly, in other iodine adequate areas, it was found that the urinary iodine concentration of pregnant women was negatively correlated with TSH, but not with FT4.[27] In contrast, no significant correlation was observed between urinary iodine concentration and any indicators of thyroid function in pregnant women from high-iodine areas.[36] The results indicate that there is no strong correlation between urinary iodine concentration and thyroid function across different trimesters in iodine-adequate or high-iodine areas. However, a correlation exists in iodine deficiency areas, particularly during the first and second trimesters. The pregnant women were divided into six groups according to the urinary iodine concentration. The results showed that, compared to the adequate iodine group, TSH levels in pregnant women with moderate to severe iodine deficiency gradually decreased as the degree of deficiency increased, while FT3, FT4, TT3, and TT4 levels gradually increased with greater iodine deficiency. There was no significant change in thyroid function among mild iodine deficiency, more-than-adequate iodine and excess iodine groups. This suggested that the correlation between iodine and thyroid function in pregnant women is most obvious when iodine is moderately and severely deficient.

Our study found that, compared to the iodine-adequate group, the incidence of thyroid dysfunction was significantly higher in the more-than-adequate iodine group. Additionally, the prevalence of hyperthyroidism and subclinical hyperthyroidism was higher in the moderate iodine deficiency group. However, there was no significant difference in thyroid dysfunction among the mild deficiency, severe deficiency, and excess iodine groups. Compared with the adequate iodine group, there was no significant difference in thyroid dysfunction between the severe iodine deficiency group and excess iodine group, which may be related to the small sample size. Further studies on the relationship between iodine and thyroid dysfunction are needed.

Epidemiological and clinical evidence regarding the relationship between iodine and thyroid autoimmunity in pregnant women is inconsistent. We found that the positive rate of TPO-Ab and the prevalence of thyroid autoimmunity in pregnant women significantly increased when iodine levels were more-than-adequate or excessive. In contrast, the positive rate of TG-Ab significantly increased in cases of iodine deficiency, indicating a U-shaped relationship among iodine deficiency, excess, and more-than-adequate iodine levels. However, there was no

correlation between urinary iodine concentration and TGAb and TPOAb titer values. This is similar to the findings of Shi et al., who found a U-shaped curve in the prevalence of TPOAb and TGAb positive in pregnant women from mild iodine deficiency to excess iodine.[37] However, a study in Shanghai found that pregnant women with iodine deficiency (UIC < 100 μg/L) had a significantly higher risk of positive TPOAb/TGAb/TRAb tests.[23] Another study evaluated the UIC values of pregnant women with and without positive TPOAb/TGAb and found that those with one or both antibodies exhibited iodine deficiency, with UIC levels significantly lower than those of women with negative antibodies, who were deemed iodine sufficient according to WHO standards.4 The inconsistent results in the above studies may be attributed to varying interpretations of TAI in pregnant women. Most previous studies have identified iodine excess as a risk factor for TAI.[38] It has been found that subjects with positive thyroid antibodies are more likely to consume non-iodized salt and less likely to consume iodine-rich foods and nutritional supplements; therefore, their iodine intake is lower, leading to iodine deficiency.[4] More than half of the subjects in this study were from rural areas with limited knowledge of TAI, and the findings were consistent with previous studies. Interestingly, iodine deficiency emerged as a risk factor for TGAb positivity. Therefore, we conclude that there may be a relationship between iodine deficiency or excess and increased thyroid autoimmunity; however, the underlying mechanisms require further investigation.

The relationship between iodine nutrition and pregnancy outcomes is controversial. Our study found that maternal iodine deficiency, more-than-adequate + excess iodine were not associated with adverse pregnancy and fetal outcomes. After adjusting for maternal age ≥35 years, primiparity, ethnicity, and thyroid disease, iodine deficiency, more-than-adequate + excess iodine were still not significantly associated with adverse pregnancy and fetal outcomes. This aligns with the results of a meta-analysis and a recent study based on birth registration data, which found that mild maternal iodine deficiency was not associated with adverse pregnancy outcomes.[14, 39] However, one study reported that the risk of preeclampsia, placenta previa, and fetal distress is low when median urinary iodine levels are between 150 - 249 μg/L, while the risk of abnormal amniotic fluid increases when median urinary iodine exceeds 250 μg/L.[40] Another study also found that maternal iodine deficiency was a risk factor for low birth weight infants.[41] The two different results may be related to varying levels of iodine deficiency or excess among pregnant women. Specifically, moderate to severe iodine deficiency or excess can lead to adverse pregnancy outcomes due to the complex relationship with iodine. The placenta, along with the thyroid, is recognized as the primary organ responsible for iodine storage in the body.[10] Iodine levels are crucial for influencing the availability of thyroid hormones in the placenta, which are essential for promoting and differentiating trophoblast cells and maintaining an anti-inflammatory environment within this organ.[11,12] Consequently, significant iodine deficiency may negatively affect the levels of thyroid hormones in the placenta, compromising placental function and leading to adverse pregnancy outcomes. Interestingly, our findings reveal a connection between moderate to severe iodine deficiency or excess and thyroid dysfunction. Subclinical hypothyroidism and hyperthyroidism emerged as independent risk factors for preterm birth and placenta previa (OR: 2.94, 95% CI: 1.16-7.45; OR: 11.5, 95% CI: 1.38-96.26). Numerous studies have supported the association between thyroid dysfunction and adverse pregnancy outcomes.[42, 43] Therefore, we recommend that future cohort studies be conducted to clarify the pathway from iodine deficiency to thyroid dysfunction and its subsequent impact on pregnancy outcomes.

Strengths and limitations

The main strengths of this study include the following aspects. Firstly, this is the first large-scale cross-sectional survey of iodine nutritional status among pregnant women in Qujing. Secondly, our study provides valuable public health data on the iodine nutritional status of pregnant women in plateau regions of China. Thirdly, our study included women across all three trimesters and categorized the subjects into six iodine nutrition levels: mild iodine deficiency, moderate iodine deficiency, severe iodine deficiency, adequate iodine, more-than-adequate iodine, and excessive iodine. The relationship between iodine and thyroid function was comprehensively evaluated. Finally, this study examines the association between the iodine nutrition of pregnant women and adverse pregnancy and fetal outcomes in the Chinese plateau region.

However, several potential limitations should be noted. First, we used on-site urine samples rather than 24-hour urine samples to assess the iodine nutritional status of pregnant women. Second, this cross-sectional study could not establish a causal relationship between maternal thyroid abnormalities and iodine status. Third, we did not monitor iodine nutrition during pregnancy or at different times after delivery in the same individuals. Finally, the study's sample size was limited, the observed area was narrow, and residual confounding could not be fully eliminated, which restricts the generalizability of the findings to all plateau regions in China. To validate our conclusions, extensive sampling investigations and studies across multiple plateau regions are necessary.

Conclusions

In conclusion, mild iodine deficiency is prevalent among pregnant women in Qujing; however, severe iodine deficiency, moderate iodine deficiency, more-than-adequate iodine, and iodine excess also exist. There were no significant differences in the distribution of iodine nutrition across the three trimesters. The relationship between iodine and thyroid function is more pronounced in pregnant women with moderate to severe iodine deficiency. More-than-adequate iodine and iodine excess are risk factors for TPO-Ab positivity and TAI, while all abnormal iodine statuses are risk factors for TG-Ab positivity. Maternal iodine nutrition was not significantly associated with adverse pregnancy and fetal outcomes in areas predominantly characterized by mild iodine deficiency. Given the U-shaped relationship between iodine levels and thyroid autoimmunity, further investigations are recommended to explore the correlation between iodine levels and the

specificity of thyroid autoantibodies. Additionally, it is advisable to enhance the monitoring of iodine nutrition among pregnant women in plateau areas and to advocate for the development of tailored iodine intake guidelines for this demographic. Furthermore, alongside iodine nutrition considerations, developing specialized iodized salt tailored to meet the unique iodine requirements of pregnant women in plateau regions could be beneficial.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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Supplementary Tables

Supplementary Table 1. Definition of thyroid disease

Thyroid diseases	1st trimester		2nd trimester		3rd trimester		Total
	TSH (mIU/L)	FT4 (pmol/L)	TSH (mIU/L)	FT4 (pmol/L)	TSH (mIU/L)	FT4 (pmol/L)	TPOAb (IU/mL) and TGAb (IU/mL)
SCH	>4.41	8.47-19.6	>4.16	5.70-14.7	>4.60	5.20-12.1	
Hypothyroidism	>4.41	<8.47	>4.16	<5.70	>4.60	<5.20	
Thyrotoxicosis	<0.02	>19.6	<0.12	>14.7	<0.45	>12.1	
Subclinical hyperthyroidism	<0.02	8.47-19.6	<0.12	5.70-14.7	<0.45	5.20-12.1	
TAI							TPOAb >16 IU/mL or TGAb >100 IU/mL

TSH, thyroid stimulating hormone; FT4, free thyroxine; TPOAb, anti-thyroid peroxidase antibody; TGAb, anti-thyroglobulin antibody; SCH, subclinical hypothyroidism; TAI, Thyroid autoimmunity.

Supplementary Table 2. Dietary habits of pregnant women under different iodine nutritional statuses

	Iodine defciency (n=609)	Iodine-adequate (n=223)	Iodine-more-than-adequate + iodine excess (n=193)	Total (n=1025)
Morning sickness				
Never	358 (58.8%)	155 (84.8%)	138 (71.5%)	651 (63.5%)
Mild	48 (7.88%)	10 (4.48%)	13 (6.74%)	71 (6.93%)
Often	71 (11.7%)	24 (10.8%)	19 (9.84%)	114 (11.1%)
Severe	132 (21.7%)	34 (15.3%)	23(11.9%)	189 (18.4%)
Dietary taste				
Moderate	467 (76.7%)	176 (78.9%)	154 (79.8%)	797 (77.8%)
Spicy and salty	58 (9.52%)	19 (8.52%)	25 (13.0%)	102 (9.95%)
Low-salt	84 (13.8%)	28 (12.6%)	14 (7.25%)	126 (12.3%)
Frequency of high iodine content foods consumption†				
Never	450 (73.9%)	148 (66.4%)	124 (64.3%)	722 (70.4%)
0.5-1 servings/week	131 (21.5%)	66 (29.6%)	43 (22.3%)	240 (23.4%)
2-3 servings/week	28 (4.60%)	9 (4.04%)	26 (13.5%)	63 (6.15%)
Frequency of dairy products consumption‡				
Never	160 (26.3%)	42 (18.8%)	30 (15.5%)	232 (22.6%)
1-3 servings/week	224 (36.8%)	70 (31.4%)	78 (40.4%)	372 (36.3%)
1 servings/day	225 (36.9%)	111 (49.8%)	85 (44.0%)	421 (41.1%)

†including kelp, seaweed and defined as 500g per serving
‡including milk and defined as 250 mL one serving

Supplementary Table 3. Association of different dietary habits and iodine nutritional statuses

	Iodine defciency				Iodine-more-than-adequate + iodine excess			
	Unadjusted OR (95%CI)	*p* value	Adjusted OR (95%CI)	*p* value	Unadjusted OR (95%CI)	*p* value	Adjusted OR (95%CI)	*p* value
Morning sickness								
Never	1.00		1.00		1.00		1.00	
Mild	2.10 (0.78-5.67)	0.144	2.00 (0.73-5.45)	0.178	1.39 (0.41-4.75)	0.601	1.33 (0.37- 4.73)	0.660
Often	1.33 (0.66- 2.67)	0.425	1.33 (0.65-2.70)	0.431	0.87 (0.35-2.18)	0.763	0.67 (0.24- 1.88)	0.450
Severe	1.73 (0.96- 3.12)	0.069	1.61 (0.87-2.99)	0.130	0.75 (0.33- 1.71)	0.491	0.76 (0.31- 1.90)	0.563
Dietary taste								
Moderate	1.00		1.00		1.00		1.00	
Spicy and salty	1.13 (0.53- 2.39)	0.753	0.91 (0.42-2.00)	0.817	1.42 (0.58- 3.46)	0.443	1.58 (0.62- 4.01)	0.341
Low-salt	1.17 (0.61- 2.23)	0.634	1.00 (0.51- 1.97)	0.998	0.59 (0.23- 1.54)	0.281	0.55 (0.20-1.56)	0.261
Frequency of high iodine content foods consumption[†]								
Never	1.00		1.00		1.00		1.00	
0.5-1 servings/week	0.66 (0.41, 1.07)	0.089	0.67 (0.41- 1.10)	0.110	0.77 (0.41- 1.45)	0.416	0.80 (0.41-1.55)	0.503
2-3 servings/week	1.20 (0.39- 3.72)	0.754	1.10 (0.35-3.49)	0.873	4.04 (1.25- 13.0)	0.019*	5.22 (1.52-17.9)	0.009*
Frequency of dairy products consumption[‡]								
Never	1.00		1.00		1.00		1.00	
1-3 servings/week	0.86 (0.47- 1.57)	0.629	0.86 (0.47-1.57)	0.620	1.55 (0.70- 3.44)	0.284	1.55 (0.67-3.60)	0.311
1 servings/day	0.55 (0.31-0.97)	0.038*	0.57 (0.32- 1.02)	0.060	1.11 (0.51- 2.38)	0.796	1.09 (0.48- 2.47)	0.837

[†]including kelp, seaweed and defined as 500g per serving
[‡]including milk and defined as 250 mL one serving

Supplementary Table 4. Characteristics and iodine nutritional status of pregnant women in urban and non-urban areas of Qujing, China

Variables	Qilin and Jingkai districts	Other districts	*p* value
N	292	333	
Age, year	28.7±4.63	28.1±4.97	0.144
Gestational week, week	15.3±8.43	15.3±7.94	0.958
Pre-pregnancy BMI, kg/m^2	21.6±1.77	21.7±1.66	0.435
Serum 25(OH)D, ng/mL	17.7±7.16	17.9±7.25	0.754
Median of urinary iodine, μg/L	124 (87.8- 192)	126 (89.0- 222)	0.263
Distribution of iodine, N (%)			0.229
Deficient	182 (62.3%)	198 (59.5%)	
Adequate	71 (24.3%)	67 (20.1%)	
More-than-adequate	28 (9.59%)	56 (16.8%)	
Excess	11 (3.77%)	12 (3.60%)	

BMI, body mass index

Supplementary Table 5. Correlations among UIC/TSH and FT3, FT4, TT3, TT4, TGAb, TPOAb in pregnant women from Qujing

	1st trimester (n=447)		2nd trimester (n=351)		3rd trimester (n=138)		Total (n=936)	
	UIC, μg/L	TSH, mIU/L	UIC, μg/L	TSH, mIU/L	UIC, μg/L	TSH, mIU/L	UIC, μg/L	TSH, mIU/L
FT3, pmol/L	-0.071	-0.336*	-0.214*	-0.238*	-0.11	-0.227*	-0.140*	-0.279*
FT4, pmol/L	-0.160*	-0.443*	-0.113*	-0.258*	-0.049	-0.348*	-0.114	-0.339*
TT3, nmol/L	-0.097*	-0.379*	-0.133*	-0.175*	-0.144	-0.171*	-0.127*	-0.272*
TT4, nmol/L	-0.12*	-0.400*	-0.144*	-0.101	-0.061	-0.064	-0.107*	-0.232*
TGAb, IU/mL	0.020	0.176*	-0.106	0.179*	-0.087	-0.312*	-0.037	0.124*
TPOAb, IU/mL	0.022	0.199*	-0.059	0.149*	0.073	-0.216	-0.001	0.147*
TSH, mIU/L	0.177*	-	0.092	-	0.072	-	0.132*	-
UIC, μg/L	-	0.177*	-	0.092	-	0.072	-	0.132*
25(OH)D, ng/mL	0.014	-0.166*	0.029	-0.174*	0.202	-0.012	0.253	-0.164*

UIC,urinary iodine concentration; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TT3,total triiodothyronine; TT4, total thyroxine; TPOAb, anti-thyroid peroxidase antibody; TGAb, anti-thyroglobulin antibody

*p<0.05 for Spearman correlation