Research of iodine status of pregnant women in the plateau area of China and the effect of iodine on thyroid function and adverse pregnancy and fetal outcomes

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ABSTRACT

Background and Objectives: This study investigated the iodine status of pregnant women at an average altitude of about 2000 meters in Qujing, China, and analyzed the relationship between iodine and thyroid function in different trimesters, as well as the relationship between iodine and adverse pregnancy and fetal outcomes. **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 nutrition with adverse pregnancy and fetal outcomes. **Results:** The median UIC was 127.2 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 positive proportion of thyroid peroxidase antibody (TPO-Ab) and the prevalence of thyroid autoimmunity (TAI) increased significantly in the iodine more than adequate and iodine excess groups. Logistic regression analysis showed maternal iodine nutrition 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 with moderate to severe iodine deficiency. Abnormal iodine nutrition 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 play a crucial role in producing 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, Qingdao and other provinces showed that pregnant women showed adequate iodine nutritional status.[5-7] However, the iodine nutritional 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 nutrition and thyroid disease distribution.[8] Regions with high altitude and low air humidity present challenges for iodine absorption and storage. Areas characterized by high altitude and low air humidity present challenges for the absorption and preservation of iodine, potentially resulting in iodine deficiency among residents of the plateau regions. Nevertheless, dietary practices specific to the plateau regions, including a preference for high-salt fare and preserved foods like ham and pickles, could contribute to higher iodine consumption among residents. Thus, there is a requirement for further exploration and analysis to ascertain the adequacy of iodine nutrition in plateau areas. Recent research indicates 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 plays a crucial role as the primary organ for iodine storage.[10] It is hypothesized that the strict control of iodine transport by the placenta is essential in protecting the fetus from excessive iodine exposure while simultaneously supporting the production of thyroid hormones by the placenta itself. 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 relation of iodine deficiency and adverse pregnancy outcomes, but reported controversial results.[13, 14] 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 relation 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 distribution characteristics of iodine nutrition status in pregnant women in plateau areas and analyze the relationship between iodine nutrition status and thyroid function, thyroid autoimmunity, and adverse pregnancy outcomes. These findings will provide reference suggestions for the monitoring and intervention of iodine nutrition status in pregnant women in plateau areas.

MATERIALS AND 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 January 1st, 2019 to August 31st, 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. And those having a previous thyroid disease (hyperthyroidism, hypothyroidism and thyroid malignancy), taking medications that may affect thyroid function (levothyroxine sodium tablets, methimazole, propylthiouracil, amiodarone, interferon alpha, lithium), having 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. Besides, a total of 936 pregnant women with complete thyroid function measurements, were studied to explore the relationship between iodine nutrition status and thyroid function in the first, second and third trimester of pregnancy. And 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.

We ensure that the manuscript incorporates the approval of an institutional review board regarding ethical considerations relevant to the submitted work.

Procedures

Information on age, ethnicity, weight, height, time of last menstrual period, number of pregnancies, self-report diseases, morning sickness, dietary taste, consuming foods with high iodine content frequency (such as kelp, seaweed, etc., defined as 500 g per serving), frequency of consumption of dairy products(such as milk, where 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) by height squared (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 tests and urinary iodine test

5 mL of fasting venous blood was taken from the subjects early in the morning, and the serum was centrifuged at room temperature to separate the serum and then the thyroid function was measured using a Sorin LIAISON-XL chemiluminescence immunoassay analyzer (Soling Diagnostics, Italy). Thyroid function measurements included the level 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.

20 mL of fasting mid-stream urine from subjects who had fasted for at least 8 hours was collected early in the morning, and the urine iodine concentration was measured by 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%. The median urinary iodine concentration was used in our analysis, to assess the iodine nutritional status of pregnant women, which was classified as iodine deficient (≤149 μg/L), iodine adequate (150-249 μg/L), iodine more than adequate (250-499 μg/L), and iodine 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 either one or more of thyroid disease during pregnancy, or 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 (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. And 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 127.2 μg/L. There were 609 (59.41%) women with iodine deficient, 223 (21.76%) women with iodine adequate, 153 (14.93%) women with iodine more than adequate, and 40 (3.90%) women with iodine excess, respectively (Table 1). There was no significant difference 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 iodine nutritional status. Among the participants, 77.76% reported consuming a

moderately flavored diet, 9.95% preferred hot and salty tastes, and 12.29% favored a bland diet. Furthermore, 70.44% of pregnant women never consumed foods high in iodine, such as kelp or seaweed (defined as 500g per serving), whereas 23.41% reported consuming 0.5-1 serving of high-iodine foods weekly, and 6.15% consumed 2-3 servings per week. Additionally, 22.63% of pregnant women avoided dairy products (e.g., milk, with 250 mL as one serving), 36.29% consumed 1-3 servings per week, and 41.07% 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=0.549, 95% CI: 0.312-0.966). 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 who consumed high-iodine foods 2-3 times weekly were likelier to experience iodine excess ($OR_{adjusted}$=5.216, 95% CI: 1.521-17.888). No significant correlation was found between dietary taste preference and iodine status in the study population (Supplementary Table 3).

Difference of iodine distribution between urban and non-urban pregnant women

Specific 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 of urinary iodine level and distribution of urinary iodine between urban and non-urban pregnant women (Supplementary Table 4).

Urinary iodine concentration and thyroid function in different stages of 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 125.9μg/L (Table 2). Serum TT3, TT4, FT3 and FT4 levels decreased significantly with the increase of pregnancy (Table 2). Participants in the third trimester were more likely to suffer from hyperthyroidism, and had higher 25(OH)D level. 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.

Association between urinary iodine concentration and thyroid function

During 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, the 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 significantly 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, for the graph of UIC and thyroid function index during pregnancy, limited cubic spline regression analysis found that UIC had a nonlinear relationship with TSH (p nonlinear = 0.048), but no nonlinear relationship with FT3, FT4, TG, TGAb and TPOAb (p nonlinear > 0.05).

Changes of thyroid function with different urinary iodine concentrations

In different groups based on urinary iodine concentration, there were no statistically significant differences in maternal age, gender, pre-pregnancy BMI, ethnicity, or primiparity. Compared with the iodine adequate group (UIC: 150-249 μg/L), serum TSH decreased in the moderate and severe iodine deficiency group, 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 iodine more than adequate and iodine excess groups. The positive proportion of TG-Ab was the lowest in the iodine adequate group, and increased significantly under other iodine concentrations (Table 3).

Compared with iodine adequate group, the abnormal rate of thyroid function in the iodine more than adequate group was higher. The proportion of TAI increased in the iodine more

than adequate group and iodine excess group. The proportions of TPO-Ab (+) and TSH (2.5mIU/L - upper limit of each pregnancy specific reference range) increased in the iodine more than adequate group. The proportion of hyperthyroidism and subclinical hyperthyroidism increased in the moderate iodine deficiency group. There was no significant difference in the proportion of SCH, hypothyroidism and hypothyroxinemia among the iodine groups (Table 3, Figure 3). There was a weak U-shaped relationship between the 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 the proportions were significantly increased in the iodine more than adequate group and iodine excess group.

Association of iodine nutrition with adverse pregnancy and fetal outcomes

There was no significant difference in maternal age, gestational age, proportion of mothers aged ≥35 years, gestational week, ethnicity, spontaneous abortion rate, 25(OH)D, hypothyroidism, SCH, hypothyroxinemia, thyrotoxicosis, subclinical hyperthyroidism, TAI, eutocia rate among iodine deficiency group, iodine adequate group and iodine more than adequate plus iodine excess group (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 is more significant in those 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 did not find any correlation between iodine deficiency, iodine more than adequate plus excess 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 125.90 μg/L (88.20 μg/L - 202.30 μg/L), and the proportion of iodine deficiency was 59.41%, and more than half of pregnant women were in mild to moderate iodine deficiency. 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, during recent years.[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 the urban and non-urban areas, indicating that there is no significant regional difference in iodine nutrition of pregnant women in Qujing, and no matter in any trimester, it is extremely important to timely monitor iodine nutrition and iodine nutrition health education for pregnant women. Furthermore, our study demonstrated that the consumption of 1-1.5 kg of high-iodine food per week may result in iodine excess. The iodine content in soil, heightened iodine requirements and excretion, coupled with insufficient knowledge of iodine nutrition in pregnant women, are likely the primary factors contributing to aberrations in iodine levels.[7, 9, 25, 26]

The research results are controversial on whether there are differences in iodine nutritional status and thyroid function of women in different periods of pregnancy. Our study found that the urinary iodine concentration of pregnant women in the three trimesters were 122.60 μg/L, 136.30 μg/L and 123.20 μg/L, respectively, and there was no significant difference in the rate of thyroid dysfunction among the three trimesters. This is consistent with the study of iodine suitable areas in Japan and the results of national surveillance data in Greece.[27, 28] However, some studies have found that the 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 increase of pregnancy. For example, the urinary iodine concentration of women in the north of Ireland during the three trimesters was 73 μg/L, 94 μg/L and 117 μg/L, respectively, showing an increasing trend.[32] A British study showed that the urinary iodine concentration of women in the first trimester, the second trimester and the third trimester were 42 μg/L, 52 μg/L and 69 μg/L, respectively, which also showed an increasing trend.[33] Overall,

for iodine adequate or mild iodine deficiency areas, the urinary iodine concentration of pregnant women in the three trimesters did not change significantly, while for iodine moderate and severe deficiency areas, the urinary iodine concentration of pregnant women may decline or increase with pregnancy. The iodine reserve of pregnant women in iodine adequate and mild iodine deficiency areas is acceptable, and there is no significant effect on the synthesis of thyroid hormone. Therefore, the urinary iodine excretion in the three trimesters is similar, and there is 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 in different periods of pregnancy. Most people pay attention to the iodine nutritional status of women in early pregnancy, which makes the urinary iodine concentration of women in early pregnancy high. With the increase of pregnancy, the attention to iodine nutrition decreases, and the urinary iodine concentration of pregnant women decreases. However, some studies have shown that in some regions, pregnant women start to take iodine supplements in the second or third trimester,[34] and dietary iodine intake, such as dairy products, increases with the increase of pregnancy,[27] resulting in the phenomenon of increased urinary iodine concentration in the second and third trimester.

Previous studies only observed the relationship between iodine nutrition and thyroid function in the first trimester, and lack of research on different pregnancy periods or different iodine nutrition 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 through the application of 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 of 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, but 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 in Tehran, the capital of Iran, 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,[35] which may be due to the local iodine appropriate area. 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 found between urinary iodine concentration and all indicators of thyroid function in pregnant women in high iodine areas.36 The results indicate that there is no strong correlation between urinary iodine concentration and thyroid function in different trimesters of pregnancy in iodine adequate or high iodine areas, but there is correlation between urinary iodine concentration and thyroid function in iodine deficiency areas, especially in the first and second trimester. Then we divided the pregnant women into six groups according to the urinary iodine concentration. The results showed that compared with the iodine adequate group, the TSH of pregnant women in the moderate and severe iodine deficiency group decreased gradually with the increase of iodine deficiency degree, while FT3, FT4, TT3 and TT4 increased gradually with the increase of iodine deficiency degree. There was no significant change in thyroid function among mild iodine deficiency, iodine more than iodine adequate and iodine excess 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 with iodine adequate group, the incidence of thyroid dysfunction in iodine more than adequate group was significantly higher, the prevalence of hyperthyroidism and subclinical hyperthyroidism in iodine moderate deficiency group was higher, while there was no significant difference in thyroid dysfunction among iodine mild deficiency group, iodine severe deficiency group and iodine excess group. Compared with the iodine adequate group, there was no significant difference in thyroid dysfunction between the severe iodine deficiency group and the iodine excess 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 for a 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 increased significantly when

iodine was more than adequate and excessive, while the positive rate of TG-Ab increased significantly when iodine was inadequate, that is, iodine deficiency, iodine more than adequate and iodine excess, showing a U-shaped relationship. 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 iodine excess.[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 UIC values of pregnant women with and without TPOAb/TGAb (+), found that UIC results of subjects with single or double positive antibodies showed iodine deficiency, which was significantly lower than that of subjects with negative antibodies, who were iodine sufficient according to WHO standards .4 The reason for the inconsistent results of the above studies may be related to the different understanding of TAI in pregnant women. Most previous studies have found that iodine excess is 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 iodine-rich 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 poor knowledge of TAI and the findings were similar to previous studies. Interestingly, iodine deficiency was found to be a risk factor for TGAb positivity in this study. Therefore, we conclude that there may be a relationship between iodine deficiency or excess and increased thyroid autoimmunity, but the underlining mechanisms needs further investigated.

The relationship between iodine nutrition and pregnancy outcomes is controversial. Our study found that maternal iodine deficiency and iodine more than adequate plus excess were not associated with adverse pregnancy and fetal outcomes. After adjusting for maternal age ≥35 years, primiparity, ethnicity, and thyroid disease, iodine deficiency and iodine more than adequate plus excess were still not significantly associated with adverse pregnancy and fetal outcomes. This was similar to the results of a meta-analysis, as well as to the results of a recent study based on birth registration collections, in which 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 the median urinary iodine is between 150~249 μg/L, while the risk of abnormal amniotic fluid is increased when the median urinary iodine is higher than 250 μg/L.[40] Another study also found that maternal iodine deficiency was a risk factor for low birth weight infants.[41] The occurrence of the two

different results may be related to pregnant women at varying levels of iodine deficiency or excess. Specifically, when there is a moderate to severe lack or excess of iodine, adverse pregnancy outcomes may arise due to the intricate relationship with iodine. The placenta, alongside the thyroid, is identified as the primary organ in the body responsible for storing iodine.[10] Iodine levels play a crucial role in influencing the availability of thyroid hormones within the placenta, which are necessary for the promotion and differentiation of cellular trophoblast cells as well as for sustaining an anti-inflammatory environment within this organ.[11, 12] Consequently, significant iodine deficiency may detrimentally impact the presence of thyroid hormones in the placenta, thereby compromising placental function and resulting in adverse pregnancy outcomes. Interestingly, our findings demonstrate a link between moderate to severe iodine deficiency/excess and thyroid dysfunction. Subclinical hypothyroidism and hyperthyroidism emerged as independent risk factors for preterm birth and placenta previa (OR: 2.944, 95% CI: 1.164-7.445; OR: 11.510, 95% CI: 1.376-96.262). Numerous studies have also supported the association between thyroid dysfunction and adverse pregnancy outcomes.[42, 43] Therefore, we suggest that future cohort studies be undertaken to elucidate the pathway from iodine deficiency to thyroid dysfunction and its consequent 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 of pregnant women in Qujing. Secondly, Our study contributes valuable public health data regarding the iodine nutritional status of pregnant women in plateau regions of China. Thirdly, our present study included women in three trimesters, and the subjects were divided 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 also comprehensively evaluated. Finally, this study examines the association of iodine nutrition of pregnant women with adverse pregnancy and fetal pregnancy outcomes in Chinese plateau area.

However, several potential limitations need to be mentioned. First, we used on-site urine samples instead of 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 track iodine nutrition during pregnancy and at different times after delivery in the same pregnant woman. Finally,

the study's sample size was limited, the observed area was narrow, and residual confounding could not be fully eliminated, thereby limiting the generalizability of the findings to all plateau regions in China. To validate our conclusions, extensive sampling investigations and studies across numerous plateau regions are necessary.

Conclusions

In conclusion, mild iodine deficiency is common among pregnant women in Qujing, but severe iodine deficiency, moderate iodine deficiency, iodine more than adequate and iodine excess also existed. There was no significant difference in the distribution of iodine nutrition among the three trimesters. The relationship between iodine and thyroid is more significant in pregnant women with moderate to severe iodine deficiency. Iodine more than adequate and iodine excess are risk factors for TPO-Ab positive and TAI, while all abnormal iodine status are risk factors for TG-Ab positive. Maternal iodine nutrition was not significantly associated with adverse pregnancy and fetal outcomes in areas with predominantly mild iodine deficiency. Given the U-shaped relationship between iodine levels and thyroid autoimmunity, it is recommended to conduct further investigations to explore the correlation between iodine levels and the specificity of thyroid autoantibodies. It is also recommended to enhance the monitoring of iodine nutrition in pregnant women residing in plateau areas and advocate for the development of tailored iodine intake guidelines for this demographic. Furthermore, in conjunction with iodine nutrition considerations, exploring the development of specialized iodized salt tailored to meet the unique iodine requirements of pregnant women in plateau regions could yield benefits.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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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	28.17±4.91	28.51±5.06	28.77±5.07	28.38±4.99	0.320
Gestational week, week	9±2.75	18.9±3.98	32.26±3.80	15.92±8.71	<0.001
Pre-pregnancy BMI, kg/m^2	21.81±1.67	21.59±1.65	21.88±1.64	21.74±1.66	0.548
Urinary iodine concentration, μg/L	123.0 (80.7, 209.0)	136.5 (95.3, 209.4)	124.2 (92.8, 227.8)	127.2 (88.3, 209.5)	0.111
Distribution of iodine, N (%)					0.490
Deficient	309 (61.43%)	216 (57.14%)	84 (58.33%)	609 (59.41%)	
Adequate	104 (20.68%)	91 (24.07%)	28 (19.44%)	223 (21.76%)	
More than adequate	69 (13.72%)	58 (15.34%)	26 (18.06%)	153 (14.93%)	
Excess	21 (4.17%)	13 (3.44%)	6 (4.17%)	40 (3.90%)	

Table 2. Revisions 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	122.60 (80.50~199.50)	136.30 (95.20~213.10)	123.20 (92.40~211.00)	0.115	125.90 (88.20~202.30)
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)[b]	3.71 (3.37~4.09)[a]	3.41 (3.14~3.97)[ab]	< 0.001*	3.84 (3.40~4.33)
FT4, pmol/L	13.10 (11.36~15.93)[b]	10.76 (9.67~12.53)[a]	10.20 (8.97~11.87)[ab]	< 0.001*	11.82 (10.21~14.20)
TT3, nmol/L	1.53 (1.38~1.80)[b]	1.44 (1.30~1.66)[a]	1.40 (1.24~1.63)[ab]	< 0.001*	1.49 (1.32~1.72)
TT4, nmol/L	90.30 (76.83~113.97)[b]	74.66 (66.84~93.98)[a]	73.91 (63.53~99.42)[a]	< 0.001*	82.52 (69.97~105.25)
TG, ng/mL	4.55 (0.38~11.40)	4.36 (0.45~9.57)	5.29 (0.21~14.65)	0.419	4.65 (0.41~10.93)
TG-Ab (+)，n (%)	126 (28.19%)	89 (25.36%)	39 (28.26%)	0.637	254 (27.14%)
TPO-Ab (+)，n (%)	196 (43.85%)	143 (40.74%)	58 (42.03%)	0.675	397 (42.41%)
Thyroid dysfunction, n (%)	272 (60.85%)	217 (61.82%)	91 (65.94%)	0.559	580 (61.97%)
SCH, n (%)	75 (15.72%)	50 (14.25%)	25 (18.12%)	0.481	150 (16.03%)
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 (13.04%)[a]	0.026*	76 (81.20%)
Subclinical hyperthyroidism, n (%)	16 (3.35%)	15 (4.27%)	0 (0.00%)	0.614	31 (3.31%)
TAI, n (%)	196 (43.85%)	143 (40.74%)	58 (42.03%)	0.675	397(42.41%)
TPOAb (+) and TSH (2.5mIU/L~upper limit of pregnancy specific reference range), n (%)	46 (10.29%)	52 (14.81%)	19 (13.77%)	0.141	117 (12.50%)
25(OH)D, ng/mL	17.12 ± 7.00[b]	18.94 ± 7.41[a]	19.56 ± 8.37[a]	0.004	18.08 ± 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.
aCompared with the 1st trimester
bCompared with the 2nd trimester
*p<0.05

Table 3. Changes of thyroid function in pregnant women under 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	27.29±4.87	28.17±5.04	28.67±4.92	28.29±4.74	28.94±5.26	29.00±5.64	0.328
BMI, kg/m^2	21.84±1.49	21.63±1.68	21.58±1.71	21.87±1.70	21.85±1.71	22.12±1.26	0.292
Gestational week, weeks	13.88±7.51	15.35±8.55	16.75±9.08	16.01±8.51	17.38±9.73	16.06±8.41	0.189
Ethnic Han, n(%)	36 (85.71%)	240 (91.60%)	238 (92.61%)	188 (92.61%)	129 (93.48%)	34 (100.00%)	0.137
Primipara, n (%)	20 (47.62%)	114 (43.51%)	125 (48.64%)	92 (45.32%)	63 (45.65%)	11 (32.35%)	0.158
TSH, mIU/L	1.66 (0.09, 3.02)[a]	1.72 (0.34, 3.08)[a]	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)[a]	3.95 (3.44, 4.45)[a]	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	13.28 (10.70, 17.08)[a]	12.11 (10.38, 15.07)[a]	11.78 (10.15, 13.95)	11.51 (10.03,13.82)	11.31 (9.52, 14.14)	11.27 (9.78, 14.03)	0.012*
TT3, nmol/L	1.62 (1.42~2.11)[a]	1.51 (1.33, 1.80)[a]	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	97.08 (70.38, 120.09)	84.12 (71.08, 109.17)	82.62 (69.82, 106.11)	80.72 (69.03, 100.44)	80.80 (66.56, 101.96)	76.67 (67.37, 108.26)	0.079
TPOAb (+), n (%)	13 (30.95%)	61 (23.28%)	49 (19.07%)	52 (25.62%)	68 (49.28%)[a]	18 (52.94%)[a]	< 0.001*
Tg Ab (+), n (%)	13 (30.95%)[a]	61 (23.28%)[a]	46 (17.90%)[a]	12 (5.91%)	52 (37.68%)[a]	17 (50.00%)[a]	< 0.001*
Thyroid dysfunction, n (%)	18 (42.86%)	126 (48.09%)	123 (47.86%)	94 (46.31%)	86 (62.32%)[a]	19 (55.88%)	0.040*
SCH, n (%)	2 (4.76%)	31 (11.83%)	55 (21.40%)	33 (16.26%)	27 (19.57%)	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 (12.60%)[a]	20 (7.78%)	12 (5.91%)	6 (4.35%)	1 (2.94%)	0.030*
Subclinical hyperthyroidism, n (%)	3 (7.14%)	15 (5.73%)[a]	8 (3.11%)	4 (1.97%)	1 (0.72%)	0 (0.00%)	0.035*
TAI, n (%)	13 (30.95%)	61 (23.28%)	49 (19.07%)	52 (25.62%)	68 (49.28%)[a]	18 (52.94%)[a]	< 0.001*
TPOAb (+) and TSH (2.5mIU/L~upper limit of pregnancy specific reference range), n (%)	3 (7.14%)	16 (6.11%)	9 (3.50%)[a]	17 (8.37%)	19 (13.77%)[a]	7 (20.59%)	< 0.001*
25(OH), ng/mL	15.28±5.76	18.02±6.88	17.78±7.43	18.21±8.01	18.35±7.45	21.15±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.
a aCompared with urinary iodine concentrations between 150 and 249ug/L
*p<0.05

Table 4. Characteristics and thyroid diseases of pregnant women followed up

Variables	Iodine defciency (n=326)	Iodine-adequate (n=115)	Iodine-more than adequate plus iodine excess (n=96)	Statistics	*p* value
Maternal age , years	28.19 ± 4.69	28.93 ± 4.97	29.26 ± 5.00	2.335	0.098
Age ≥ 35 years, n (%)	34 (10.43%)	16 (13.91%)	17 (17.71%)	3.875	0.144
BMI, kg/m^2	21.52 ± 1.68[b]	21.96±1.77[a]	22.00±1.69[a]	4.628	0.010*
Gestational week, weeks	15.26 ± 8.34	15.81±8.35	16.22±8.37	0.559	0.572
Ethnic Han, n (%)	300 (92.02%)	106 (92.17%)	91 (94.79%)	0.854	0.652
Primipara, n (%)	151 (46.32%)	52 (45.22%)	41 (42.71%)	0.393	0.822
25(OH)D, ng/mL	17.70 ± 7.21	18.03±7.72	19.23±7.34	1.123	0.326
Vitamin D deficiency, n (%)	215 (65.95%)	72 (62.61%)	52 (54.17%)	4.441	0.109
UIC, μg/L	95.95 (69.28~117.33)[b]	187.40 (164.20~215.60)[a]	348.30 (304.75~472.65)[ab]	407.756	<0.001*
Hypothyroidism, n(%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	-	-
SCH, n(%)	39 (11.96%)	18 (15.65)	15 (15.63%)	1.491	0.474
Hypothyroxinemia, n (%)	4 (1.23%)	1 (0.87%)	0 (0.00%)	-	-
Thyrotoxicosis, n (%)	30 (9.20%)[b]	1 (0.87%)[a]	2 (2.08%)[a]	-	-
Subclinical hyperthyroidism, n (%)	18 (5.52%)	4 (3.48%)	2 (2.08%)	-	-
TAI, n (%)	56 (17.18%)	12 (10.43%)	10 (10.42%)	2.390	0.303
Eutocia , n (%)	199 (61.04%)	61 (53.04%)	54 (56.25%)	2.478	0.290

BMI, Body Mass Index; UIC, urinary iodine concentration; SCH, subclinical hypothyroidism; TAI, Thyroid autoimmunity.
a Compared with the iodine deficiency group
bCompared 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 (21.74%)	1 [Reference]			
Deficiency	326	89 (27.30%)	1.402 (0.840-2.339)	0.196	1.453 (0.859-2.457)	0.164
More than adequate plus excess	96	21 (21.88%)	1.195 (0.624-2.287)	0.592	1.172 (0.607-2.261)	0.636
HDP						
Adequate	115	2 (1.74%)	1 [Reference]			
Deficiency	326	10 (3.07%)	1.788 (0.368-8.285)	0.458	1.910 (0.406-8.985)	0.413
More than adequate plus excess	96	1 (1.04%)	0.595 (0.053-6.661)	0.673	0.613 (0.054-6.935)	0.692
Premature delivery						
Adequate	115	4 (3.48%)	1 [Reference]			
Deficiency	326	14 (4.29%)	1.245 (0.401-3.863)	0.704	1.601 (0.497-5.156)	0.430
More than adequate plus excess	96	3 (3.13%)	0.895 (0.195-4.101)	0.887	0.765 (0.161-3.633)	0.736
Abortion						
Adequate	115	6 (5.22%)	1 [Reference]			
Deficiency	326	11 (3.37%)	0.634 (0.229-1.758)	0.381	0.689 (0.241-1.968)	0.487
More than adequate plus excess	96	9 (9.38%)	1.879 (0.644-5.483)	0.248	1.986 (0.668-5.908)	0.217
Abnormal amniotic fluid						
Adequate	115	3 (2.61%)	1 [Reference]			
Deficiency	326	14 (4.29%)	1.675 (0.473-5.938)	0.424	1.579 (0.432-5.771)	0.489
More than adequate plus excess	96	3 (3.13%)	1.204 (0.237-6.108)	0.822	1.147 (0.222-5.934)	0.870
Cord entanglement						
Adequate	115	1 (0.87%)	1 [Reference]			
Deficiency	326	3 (0.92%)	1.059 (0.109-10.282)	0.961	1.155 (0.103-12.982)	0.907
More than adequate plus excess	96	1 (1.04%)	1.200 (0.074-19.443)	0.898	1.679 (0.095-29.755)	0.724
Placenta previa						
Adequate	115	1 (0.87%)	1 [Reference]			
Deficiency	326	3 (0.92%)	1.059 (0.109-10.282)	0.961	0.738 (0.063-8.601)	0.808
More than adequate plus excess	96	3 (3.13%)	3.677 (0.376-35.941)	0.263	4.107 (0.389-43.330)	0.240
Fetal distress						
Adequate	115	6 (5.22%)	1 [Reference]			
Deficiency	326	18 (5.52%)	1.062 (0.411-2.744)	0.902	1.093 (0.414-2.888)	0.857
More than adequate plus excess	96	1 (1.04%)	0.191 (0.023-1.617)	0.129	0.179 (0.021-1.530)	0.116
Macrosomia						
Adequate	115	2 (1.74%)	1 [Reference]			
Deficiency	326	7 (2.15%)	1.240 (0.254-6.056)	0.791	1.359 (0.274-6.745)	0.707
More than adequate plus excess	96	0 (0.00%)	-	-	-	-

HDP, hypertensive disease during pregnancy.
-: Not statistically analyzed because of small sample size; *p<0.05
Model 1: Univariable logistic regression analysis

Model 2: Adjusted for age⩾35 years, primiparity, ethnicity, thyroid disease
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
*$p<0.05$

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	8.47~19.60	>4.16	5.70~14.70	>4.60	5.20~12.10	
Hypothyroidism	>4.41	<8.47	>4.16	<5.70	>4.60	<5.20	
Thyrotoxicosis	<0.02	>19.60	<0.12	>14.70	<0.45	>12.1	
Subclinical hyperthyroidism	<0.02	8.47~19.60	<0.12	5.70~14.70	<0.45	5.20~12.10	
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 and iodine excess (n=193)	Total（n=1025）
Morning sickness				
Never	358 (58.78%)	155 (84.75%)	138 (71.50%)	651 (63.51%)
Minor	48 (7.88%)	10 (4.48%)	13 (6.74%)	71 (6.93%)
Generally	71 (11.66%)	24 (10.76%)	19 (9.84%)	114 (11.12%)
Serious	132 (21.67%)	34 (15.25%)	23(11.92%)	189 (18.44%)
Dietary taste				
Moderate	467 (76.68%)	176 (78.92%)	154 (79.79%)	797 (77.76%)
Spicy and salty	58 (9.52%)	19 (8.52%)	25 (12.95%)	102 (9.95%)
Low-salt	84 (13.79%)	28 (12.56%)	14 (7.25%)	126 (12.29%)
Consuming foods with high iodine content frequency (such as kelp, seaweed, etc., defined as 500g per serving)				
Never	450 (73.89%)	148 (66.37%)	124 (64.25%)	722 (70.44%)
0.5-1 servings/week	131 (21.51%)	66 (29.60%)	43 (22.28%)	240 (23.41%)
2-3 servings/week	28 (4.60%)	9 (4.04%)	26 (13.47%)	63 (6.15%)
Frequency of consumption of dairy products (such as milk, where 250 mL is considered as one serving)				
Never	160 (26.27%)	42 (18.83%)	30 (15.54%)	232 (22.63%)
1-3 servings/week	224 (36.78%)	70 (31.39%)	78 (40.41%)	372 (36.29%)
1 servings/day	225 (36.94%)	111 (49.78%)	85 (44.04%)	421 (41.07%)

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

	Iodine defciency				Iodine-more than adequate and 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	
Minor	2.098 (0.776, 5.674)	0.144	1.996 (0.730, 5.453)	0.178	1.389 (0.406, 4.747)	0.601	1.330 (0.374, 4.732)	0.660
Generally	1.329 (0.661, 2.674)	0.425	1.330 (0.654, 2.702)	0.431	0.868 (0.345, 2.181)	0.763	0.672 (0.240, 1.882)	0.450
Serious	1.728 (0.958, 3.118)	0.069	1.613 (0.869, 2.993)	0.130	0.749 (0.329, 1.705)	0.491	0.764 (0.307, 1.903)	0.563
Dietary taste								
Moderate	1.00		1.00		1.00		1.00	
Spicy and salty	1.128 (0.532, 2.394)	0.753	0.912 (0.416, 1.999)	0.817	1.418 (0.581, 3.462)	0.443	1.575 (0.618, 4.013)	0.341
Low-salt	1.170 (0.613, 2.232)	0.634	0.999 (0.507, 1.967)	0.998	0.591 (0.227, 1.538)	0.281	0.551 (0.195, 1.557)	0.261
Consuming foods with high iodine content frequency								
Never	1.00		1.00		1.00		1.00	
0.5-1 servings/week	0.658 (0.406, 1.067)	0.089	0.669 (0.409, 1.096)	0.110	0.767 (0.405, 1.453)	0.416	0.798 (0.412, 1.545)	0.503
2-3 servings/week	1.198 (0.386, 3.718)	0.754	1.099 (0.346, 3.488)	0.873	4.036 (1.253, 12.998)	0.019*	5.216 (1.521, 17.888)	0.009*
Frequency of consumption of dairy products								
Never	1.00		1.00		1.00		1.00	
1-3 servings/week	0.863 (0.474, 1.570)	0.629	0.858 (0.467, 1.573)	0.620	1.548 (0.696, 3.442)	0.284	1.547 (0.665, 3.599)	0.311
1 servings/day	0.549 (0.312, 0.966)	0.038*	0.570 (0.318, 1.023)	0.060	1.106 (0.514, 2.381)	0.796	1.090 (0.482, 2.465)	0.837

Foods with high iodine content frequency: (such as kelp, seaweed, etc., defined as 500g per serving)
Frequency of consumption of dairy products (such as milk, where 250 mL is considered as 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	28.67±4.63	28.11±4.97	0.144
Gestational week, week	15.25±8.43	15.29±7.94	0.958
Pre-pregnancy BMI, kg/m^2	21.60±1.77	21.71±1.66	0.435
Serum 25(OH)D, ng/mL	17.65±7.16	17.87±7.25	0.754
Median of urinary iodine, μg/L	123.55 (87.80, 191.73)	125.8 (88.95, 222.10)	0.263
Distribution of iodine, N (%)			0.229
Deficient	182 (62.33%)	198 (59.46%)	
Adequate	71 (24.32%)	67 (20.12%)	
More than adequate	28 (9.59%)	56 (16.82%)	
Excess	11 (3.77%)	12 (3.60%)	

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

	1st trimester(n=447)		2st trimester(n=351)		3st 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	-0.16*	-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

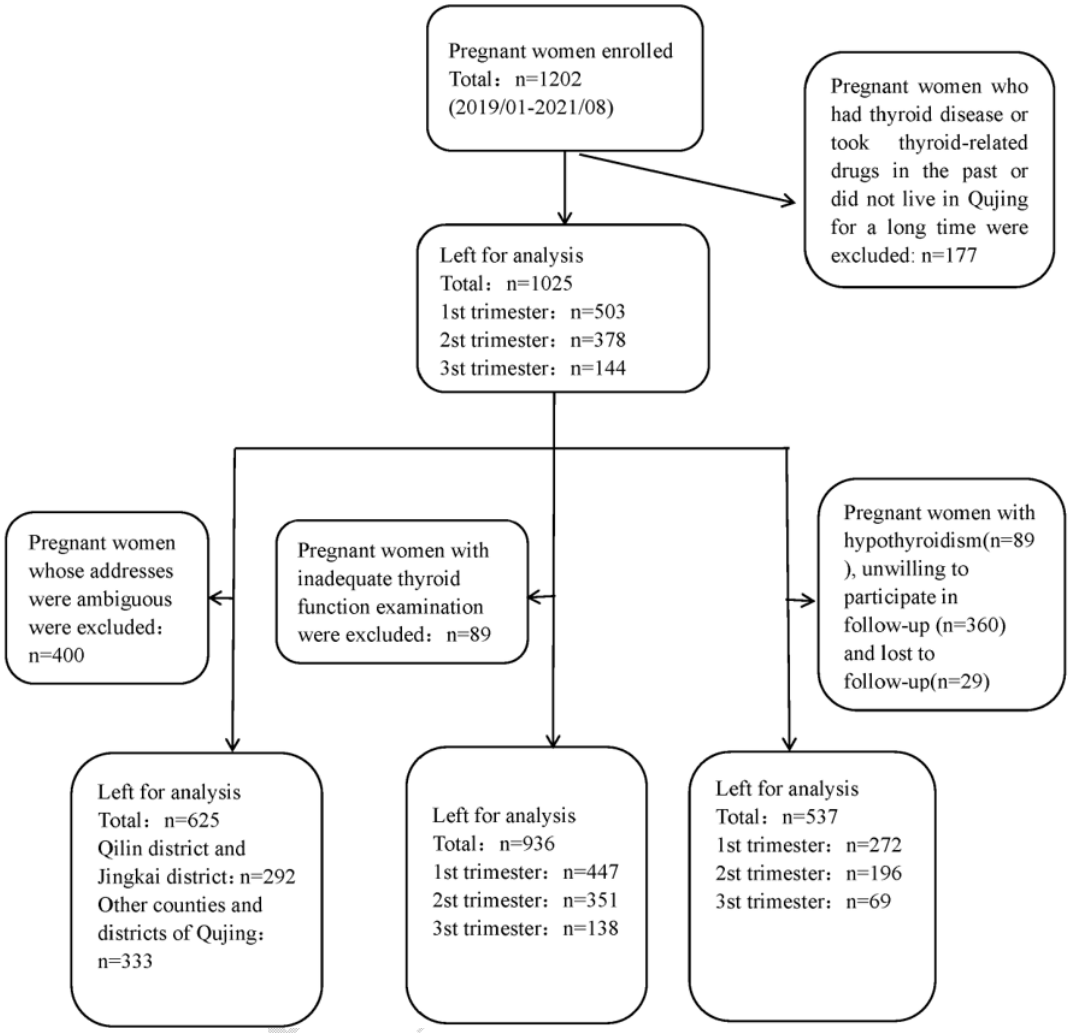

Figure 1. Flow chart of participant

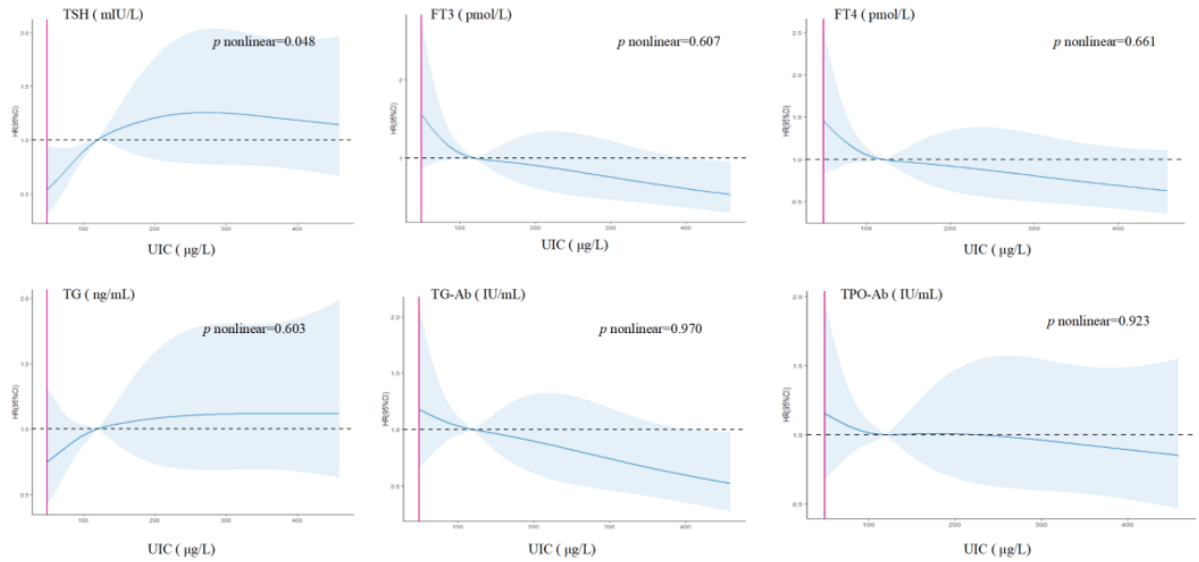

Figure 2. Limited cubic spline analysis of urinary iodine concentration on thyroid function in pregnant women. UIC,urinary iodine concentration; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TG,thyroglobulin; TG-Ab, anti-thyroglobulin antibody; TPO-Ab, anti-thyroid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

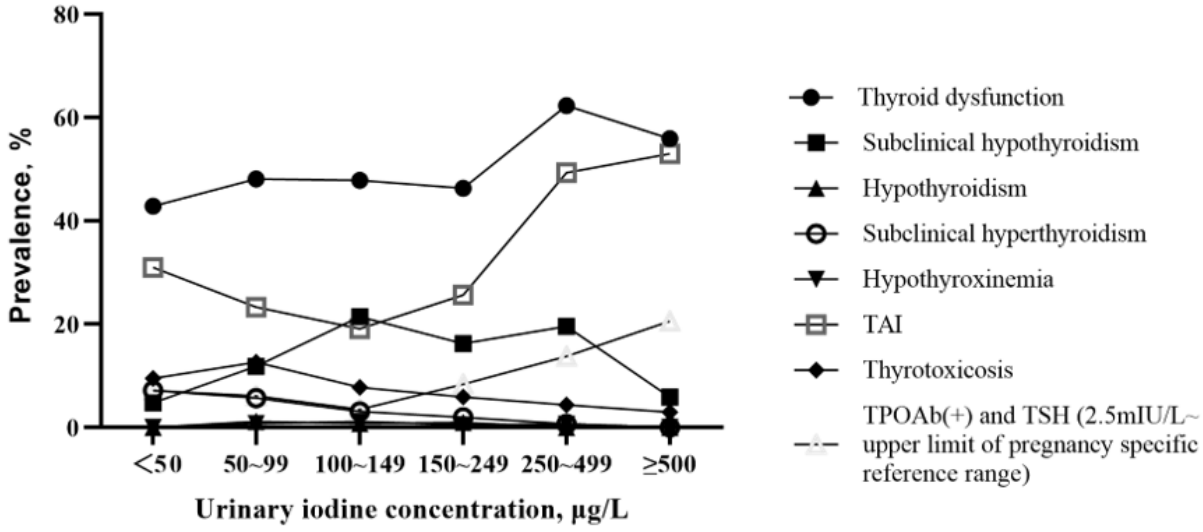

Figure 3. Changes of thyroid diseases in pregnant women under different urinary iodine concentrations