Relationship between thyroid disorders and uterine fibroids among reproductive-age women

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Abstract. Uterine fibroids and thyroid nodules, both of which are crucially affected by estrogen, are common diseases among reproductive-age women. However, little attention has been paid to the association between the two diseases. This retrospective case-control study aimed to assess the relationships among thyroid nodules, thyroid function and uterine fibroids in China. We reviewed the electronic records of 853 reproductive-age women who attended health check-ups at the Second Affiliated Hospital of Wenzhou Medical University from July 1st, 2017, to June 30th, 2018. All subjects received transvaginal pelvic ultrasound, thyroid ultrasound, thyroid function, and other laboratory tests. We found that the prevalence of thyroid nodules in subjects with uterine fibroids was remarkably higher than that in subjects without fibroids. The proportion of thyroid nodules ≥1 cm in subjects with uterine fibroids was significantly higher than that in subjects without fibroids. Women with thyroid nodules had a higher proportion of multiple uterine fibroids than women without thyroid nodules. Among the parameters of thyroid function, the only statistically significant parameter was total triiodothyronine, i.e., women with uterine fibroids had lower total triiodothyronine levels than unaffected controls; however, the total triiodothyronine levels were within the normal ranges. Moreover, no significant difference was noted in thyroid hormone status between subjects with and without uterine fibroids. Our findings suggest that thyroid nodules are positively correlated with uterine fibroids among reproductive-age women in China. Further studies are needed to confirm this association and fully understand the common pathogenetic mechanism underlying the association between uterine fibroids and thyroid nodules.

Key words: China, Reproductive-age women, Thyroid function, Thyroid nodules, Uterine fibroids
function and uterine fibroids in a population of reproductive-age women in China.

Methods

Study subjects and design

In this research, we retrospectively reviewed the electronic records of 853 reproductive-age women aged 24 to 51 years who attended health check-ups at the Second Affiliated Hospital of Wenzhou Medical University from July 1st, 2017 to June 30th, 2018. All participating women received a general medical examination consisting of anthropometric data, thyroid ultrasound, transvaginal pelvic ultrasound, thyroid function parameters, and other laboratory tests. In addition, we also assessed the following demographic and clinical information for each subject: age, menopausal status, general condition, medication history, and surgical history if any. Subjects were excluded from the analysis according to the following criteria: 1) nonaccess, pregnancy, lactation or menopause; 2) a history of thyroid surgery (either partial or complete thyroidectomy); 3) a history of myomectomy or hysterectomy; 4) a history of taking amiodarone or hormonal therapy (sex hormones, mineralocorticoids, or glucocorticoids); 5) a history of head and neck radiotherapy; 6) severe infection or significant neurological or psychological disorders (depression, anxiety, and schizophrenia); 7) diagnosis of several severe diseases such as cardiac failure, malignancies, and hepatic or renal insufficiency diseases; and 8) a history of other endocrine diseases or autoimmune disorders (polycystic ovarian syndrome, type 1 diabetes mellitus, systemic lupus erythematosus and so on). Ethical approval was given by the Ethical Committee of the Second Affiliated Hospital of Wenzhou Medical University (No. LW-20170018). All participants gave informed consent before starting this study.

Anthropometric indices

By reviewing the electronic medical records, we recorded the anthropometric indices of the participating women, and these data consisted of height (m), weight (kg), and blood pressure (systolic blood pressure, SBP; diastolic blood pressure, DBP). In addition, the body mass index (BMI) was calculated as weight (kg)/height (m²).

Ultrasound measurements

In this study, two experienced sonographers performed thyroid and transvaginal ultrasound examinations. All subjects were examined for uterine fibroids by gynecologic ultrasound using GE Voluson™ E6, E8 or E10 ultrasound systems (GE Medical Systems, American) with a transvaginal probe (frequency, 7~10 MHz). Diagnosis of uterine fibroids was made through ultrasound results, defined as a mass with a ≥0.5 cm diameter [17]. According to the results of transvaginal ultrasound, 432 individuals were recruited as having a diagnosis of at least one uterine fibroid, and 421 participants with a normal, fibroid-free uterine structure on ultrasound were selected at the same period as controls for this study. For each case subject, the location of the largest fibroid (anterior wall, posterior wall, lateral wall, or fundus), the type of the largest fibroid (intramural, subserous or submucous fibroid), the size of the largest fibroid (<3 cm diameter as small or ≥3 cm diameter as large) and the number of fibroids (only one fibroid as single or a fibroid number of ≥2 as multiple) were also recorded. Furthermore, we calculated the volume of the largest fibroid using the ellipsoid formula \((\pi \times \text{length} \times \text{width} \times \text{height})/6\).

In the same period, thyroid ultrasonography was performed to detect thyroid nodules using a high-resolution ultrasound system and 7.5 MHz transducers (Philips Ultrasound, USA). The diagnostic criterion of thyroid nodules by ultrasound is a discrete lesion within the thyroid gland that is radiologically different from the surrounding thyroid parenchyma [18]. Women with thyroid nodules >0.2 cm were considered positive. According to ultrasonography reports, participants were split into the thyroid-nodule-present group and the thyroid-nodule-absent group. The largest diameter of the thyroid nodule was considered the main nodule; therefore, the greatest nodule dimension was recorded as the index of the thyroid nodule size [19]. For each subject with thyroid nodules, the number of nodules (single or multiple), the largest diameter of the nodules (<1 cm or ≥1 cm), and the internal content (composition) of the nodules (solid nodules, cystic nodules or complex nodules) were reported. The Thyroid Imaging Reporting and Data System (TIRADS) is a risk stratification system for classifying thyroid nodules on ultrasound. TIRADS is subclassified into the following categories: TIRADS 1 (normal thyroid gland); TIRADS 2 (benign lesions); TIRADS 3 (probably benign lesions); TIRADS 4 (suspicious lesions); TIRADS 5 (probably malignant lesions); and TIRADS 6 (biopsy-proven malignancy) [20]. Therefore, the TIRADS classification was reported based on the thyroid nodule ultrasound findings in this study.

Laboratory analyses

Meanwhile, all women provided a blood sample of the cubital vein in the early morning after fasting, to measure the serum levels of fasting plasma glucose (FPG, mmol/L), lipid parameters comprising the levels of total cholesterol (TC, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), and triglycerides (TG, mmol/L), cholesterol (LDL-C, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), and triglycerides (TG, mmol/L), and these data consisted of height (m), weight (kg), and blood pressure (systolic blood pressure, SBP; diastolic blood pressure, DBP). In addition, the body mass index (BMI) was calculated as weight (kg)/height (m²).
mmol/L), as well as thyroid function parameters including TSH (μIU/mL), free triiodothyronine (FT3, pg/mL), free thyroxine (FT4, ng/dL), total triiodothyronine (TT3, ng/mL), and total thyroxine (TT4, μg/dL). Measurements of FPG and lipid parameter levels were performed using an automated biochemical analyzer, and thyroid function parameters were measured using electrochemiluminescence immunoassays on a Cobas e601 fully automated analyzer (Roche Diagnostic, Germany). The analytical intra- and interassay coefficients of variation were less than 10%.

In our hospital, the normal range for FPG was 3.9–6.1 mmol/L; for TC, 3.10–5.20 mmol/L; for TG, 0.70–1.70 mmol/L; for HDL-C, 0.78–1.96 mmol/L; and for LDL-C, 2.07–3.10 mmol/L. In addition, the normal reference ranges were 0.55–4.78 μIU/mL for TSH, 2.30–4.20 pg/mL for FT3, 0.89–1.76 ng/dL for FT4, 0.60–1.81 ng/mL for TT3 and 4.50–10.90 μg/dL for TT4. Euthyroidism was defined as TSH, FT3 and FT4 levels within the normal reference range. The criteria for overt hypothyroidism included a TSH level of >4.78 μIU/mL and a lower-than-normal values of FT3 or/and FT4. A TSH level of >4.78 μIU/mL and FT3 and FT4 within the normal reference range was accepted as subclinical hypothyroidism. Overt hyperthyroidism was defined as a TSH level of <0.55 μIU/mL and higher-than-normal values of FT3 or/and FT4. Subclinical hyperthyroidism was defined as a TSH level of <0.55 μIU/mL with FT3 and FT4 within the normal reference range.

### Statistical analysis

Statistical analysis of the acquired data was conducted using Statistics Package for Social Sciences for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Demographic and anthropometric indices and other clinical parameters are reported as numbers (frequencies) for categorical variables and as the mean ± standard deviation (SD) or medians (25th percentile, 75th percentiles) for continuous variables. Additionally, intergroup comparisons for continuous variables were evaluated by the Mann-Whitney U-test or independent samples t-test, and categorical variables were compared with the Chi-square test. Furthermore, we calculated the odds ratio (OR) with 95% confidence intervals (95% CI) for the correlation between thyroid nodules and uterine fibroids. Results with p < 0.05 were considered significant.

### Results

This study selected a total of 853 reproductive-age women, including 432 women with uterine fibroids (referred to as the fibroid group) and 421 women without uterine fibroids (designated as the control group). The baseline characteristics of the participating women with and without uterine fibroids are summarized in Table 1. There were no statistically significant differences between the two groups with regards to age, weight, height, BMI, blood pressure (SBP and DBP), or biochemical parameters including FPG, TC, HDL-C, and LDL-C (all p > 0.05), implying that the data of these two groups were comparable.

#### Table 1  Clinical characteristics of subjects with and without uterine fibroids

| Variable     | Subjects with fibroids (n = 432) | Subjects without fibroids (n = 421) | p values |
|--------------|----------------------------------|------------------------------------|----------|
| Age (years)  | 43.29 ± 4.80                     | 42.76 ± 4.90                      | 0.07     |
| Weight (kg)  | 57.01 ± 8.02                     | 56.39 ± 7.76                      | 0.50     |
| Height (m)   | 1.58 ± 0.05                      | 1.58 ± 0.05                       | 0.32     |
| BMI (kg/m²)  | 22.71 ± 2.96                     | 22.56 ± 2.86                      | 0.60     |
| SBP (mmHg)   | 118.26 ± 15.75                   | 117.71 ± 17.36                    | 0.29     |
| DBP (mmHg)   | 72.09 ± 11.80                    | 71.11 ± 12.18                     | 0.23     |
| FPG (mmol/L) | 5.06 ± 1.17                      | 5.03 ± 0.65                       | 0.17     |
| TG (mmol/L)  | 1.31 ± 0.80                      | 1.26 ± 0.75                       | 0.28     |
| TC (mmol/L)  | 5.13 ± 0.96                      | 5.11 ± 1.01                       | 0.25     |
| HDL-C (mmol/L)| 1.39 ± 0.34                     | 1.39 ± 0.34                       | 0.91     |
| LDL-C (mmol/L)| 2.75 ± 0.77                     | 2.75 ± 0.88                       | 0.37     |

Data are provided as the mean ± standard deviation. p < 0.05 was considered statistically significant.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
The prevalence of thyroid nodules in subjects with uterine fibroids (65.28%) was significantly higher than that in subjects without uterine fibroids (52.73%) ($\chi^2 = 13.88$, OR = 1.69, 95% CI, 1.28–2.22, $p < 0.001$) (Table 2).

In our study, the 504 participants with thyroid nodules consisted of 282 women with uterine fibroids and 222 women without uterine fibroids. To further investigate the relationship between uterine fibroids and thyroid nodule-related factors, several ultrasonographic characteristics of the thyroid nodules (i.e., number, sizes, internal content, and TIRADS classification) were compared between groups of subjects with and without uterine fibroids. The results showed that no significant differences were noted in nodule number, internal content (composition) of nodules, and TIRADS classification between these two groups ($\chi^2 = 0.23$, $p = 0.63$; $\chi^2 = 1.34$, $p = 0.51$; $\chi^2 = 0.56$, $p = 0.76$, respectively). The only statistically significant parameter was the nodule size, i.e., the distribution of thyroid nodule sizes larger than 1 cm in subjects with uterine fibroids (25.53%) was significantly higher than that in subjects without uterine fibroids (17.57%) ($\chi^2 = 4.59$, $p = 0.03$) (Table 3).

As shown in Table 4, the 432 subjects with uterine fibroids included 282 subjects with thyroid nodules and 150 subjects without thyroid nodules. The association between thyroid nodules and the ultrasonographic characteristics of uterine fibroids was also investigated, including the uterine fibroid number and the diameter, volume, size, location, and type of the largest uterine fibroid. Our results showed that multiple fibroids were present in 57.09% of subjects with thyroid nodules and 42% of subjects without thyroid nodules, which was statistically significant ($\chi^2 = 8.93$, $p = 0.003$). Nevertheless, there were no statistically significant between-group differences with regard to uterine fibroid maximum diameter, volume, size (small/large), location (anterior, posterior, lateral, and fundus), or type (intramural, subserous and submucous) (1.70 (1.00, 2.60) versus 1.50 (1.00, 2.50), $p = 0.24$; 1.59 (0.28, 5.90) versus 1.03 (0.21, 5.08), $p = 0.19$; $\chi^2 = 0.09$, $p = 0.77$; $\chi^2 = 2.78$, $p = 0.43$; $\chi^2 = 0.91$, $p = 0.61$, respectively).

Additionally, we also compared the parameters of thyroid function (TT3, TT4, FT3, FT4, and TSH) of

Table 2  The prevalence of thyroid nodules in subjects with and without uterine fibroids

| Variable                  | Subjects with thyroid nodules | Subjects without thyroid nodules | Total | $\chi^2$ values | $p$ values |
|---------------------------|------------------------------|---------------------------------|-------|----------------|------------|
| Subjects with fibroids    | 282 (65.28%)                | 150 (34.72%)                   | 432   | 13.88          | 0.000*     |
| Subjects without fibroids | 222 (52.73%)                | 199 (47.27%)                   | 421   |                |            |
| Total                     | 504                         | 349                             | 853   |                |            |

Data are provided as numbers (frequencies). $p < 0.05$ was considered statistically significant. * $p < 0.05$.

Table 3  Comparison of the thyroid ultrasonography characteristics of subjects with and without uterine fibroids ($n = 504$)

| Variable                              | Subjects with fibroids ($n = 282$) | Subjects without fibroids ($n = 222$) | $p$ values |
|---------------------------------------|-----------------------------------|--------------------------------------|------------|
| Number of nodules                     |                                   |                                      |            |
| single thyroid nodule                 | 116 (41.13%)                      | 96 (43.24%)                          | 0.63       |
| multiple thyroid nodules              | 166 (58.87%)                      | 126 (56.76%)                         |            |
| Nodule size                           |                                   |                                      |            |
| <1 cm                                 | 210 (74.47%)                      | 183 (82.43%)                         | 0.03*      |
| $\geq$1 cm                            | 72 (25.53%)                       | 39 (17.57%)                          |            |
| Internal content (composition) of the nodules |                              |                                      |            |
| solid nodule                          | 191 (67.73%)                      | 150 (67.57%)                         | 0.51       |
| cystic nodule                         | 75 (26.60%)                       | 64 (28.83%)                          |            |
| complex nodule                        | 16 (5.67%)                        | 8 (3.60%)                            |            |
| TIRADS classification                 |                                   |                                      |            |
| TIRADS 2                              | 84 (29.79%)                       | 69 (31.08%)                          | 0.76       |
| TIRADS 3                              | 172 (60.99%)                      | 129 (58.11%)                         |            |
| TIRADS 4                              | 26 (9.22%)                        | 24 (10.81%)                          |            |

Data are provided as numbers (frequencies). $p < 0.05$ was considered statistically significant. * $p < 0.05$.

TIRADS, Thyroid Imaging Reporting and Data System. As TIRADS 1 indicates a normal thyroid gland, the TIRADS classification (TIRADS 2, TIRADS 3, TIRADS 4) was reported based on the thyroid nodule ultrasound findings in this study.
subjects exhibiting uterine fibroids with those not exhibiting uterine fibroids to determine the correlation between thyroid function and uterine fibroids. Our findings showed that women with uterine fibroids had lower serum TT3 levels than the women in the control group (1.01 (0.92, 1.12) versus 1.04 (0.93, 1.14), p = 0.02). Nevertheless, there was no different relationship tendency with regard to the levels of TT4, FT4, FT3, or TSH between groups of subjects with and without uterine fibroids (p > 0.05). Furthermore, these participants were divided into different subgroups according to thyroid hormone status (euthyroidism, overt hypothyroidism, subclinical hypothyroidism, overt hyperthyroidism, subclinical hyperthyroidism). The analysis results indicated that there was no significant difference in thyroid hormone status between the groups of subjects with and without uterine fibroids (p = 0.29) (Table 5).

### Table 4  Comparison of the uterine fibroid ultrasonography characteristics of subjects with and without thyroid nodules (n = 432)

| Variable                        | Subjects with thyroid nodules (n = 282) | Subject without thyroid nodules (n = 150) | p values |
|---------------------------------|----------------------------------------|------------------------------------------|----------|
| Diameter of the largest fibroid (cm) | 1.70 (1.00, 2.60)                      | 1.50 (1.00, 2.50)                        | 0.24     |
| Volume of the largest fibroid (cm³) | 1.59 (0.28, 5.90)                      | 1.03 (0.21, 5.08)                        | 0.19     |
| Size of the largest fibroid     |                                        |                                          |          |
| small (<3 cm diameter)          | 226 (80.14%)                           | 122 (81.33%)                             | 0.77     |
| large (≥3 cm diameter)          | 56 (19.86%)                            | 28 (18.67%)                              |          |
| Fibroid number                  |                                        |                                          |          |
| single fibroid                  | 121 (42.91%)                           | 87 (58%)                                 | 0.003*   |
| multiple fibroids               | 161 (57.09%)                           | 63 (42%)                                 |          |
| Location of the largest fibroid |                                        |                                          |          |
| anterior                        | 130 (46.10%)                           | 64 (42.67%)                              | 0.43     |
| posterior                       | 90 (31.91%)                            | 54 (36%)                                 |          |
| lateral                         | 44 (15.60%)                            | 18 (12%)                                 |          |
| fundal                          | 18 (6.38%)                             | 14 (9.33%)                               |          |
| Type of the largest fibroid     |                                        |                                          |          |
| subserous                       | 14 (4.96%)                             | 5 (3.33%)                                | 0.61     |
| intramural                      | 264 (93.62%)                           | 144 (96%)                                |          |
| submucous                       | 4 (1.42%)                              | 1 (0.67%)                                |          |

Data are provided as medians (25th percentile, 75th percentiles) or numbers (frequencies) as appropriate. * p < 0.05.

### Table 5  Comparison of thyroid function of subjects with and without uterine fibroids

| Variable          | Subjects with fibroids (n = 432) | Subjects without fibroids (n = 421) | p values |
|-------------------|----------------------------------|-------------------------------------|----------|
| Thyroid hormones levels |                                   |                                     |          |
| TT3 (ng/mL)       | 1.01 (0.92, 1.12)                | 1.04 (0.93, 1.14)                   | 0.02*    |
| TT4 (μg/dL)       | 7.81 (6.93, 8.68)                | 7.80 (6.94, 8.67)                   | 0.94     |
| FT3 (pg/mL)       | 3.12 (2.91, 3.35)                | 3.15 (2.93, 3.35)                   | 0.29     |
| FT4 (ng/dL)       | 1.25 (1.16, 1.34)                | 1.25 (1.16, 1.34)                   | 0.89     |
| TSH (μIU/mL)      | 1.77 (1.31, 2.51)                | 1.82 (1.34, 2.50)                   | 0.64     |
| Thyroid hormone status |                                 |                                     |          |
| Euthyroidism      | 410 (94.91%)                     | 387 (91.92%)                        | 0.29     |
| Overt hypothyroidism | 1 (0.23%)                       | 1 (0.24%)                           |          |
| Subclinical hypothyroidism | 10 (2.31%)                    | 15 (3.56%)                          |          |
| Overt hyperthyroidism | 4 (0.93%)                       | 3 (0.71%)                           |          |
| Subclinical hyperthyroidism | 7 (1.62%)                     | 15 (3.56%)                          |          |

Data are provided as medians (25th percentile, 75th percentiles) or numbers (frequencies) as appropriate. * p < 0.05.

TT3, total triiodothyronine; TT4, total thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.
Discussion

This case-control study focused on the possible relationship between thyroid nodules, thyroid function and uterine fibroids among reproductive-age women in China. Our findings indicated that the prevalence of thyroid nodules in subjects with uterine fibroids was remarkably higher than that in subjects without uterine fibroids.

Uterine fibroids and thyroid nodules are important public health problems in the general population. To date, little attention has been paid to the association between uterine myoma and thyroid nodules. In 2007, a study conducted in southwestern Greece by Spinos et al. [12] included 80 women with symptoms of fibroids and 40 women with a normal uterine morphology to cross-sectionally determine the incidence of thyroid nodules in subjects with leiomyoma. All subjects were examined by ultrasound, and those with thyroid nodules >1 cm were regarded as positive. The results showed that the frequency of solitary thyroid nodules was 38.7% in subjects with uterine fibroids and 20% in subjects with a normal uterus; the researchers thus concluded that women with leiomyoma had an increase in the frequency of solitary thyroid nodules. However, this study did not further analyze the association between uterine myoma and thyroid nodule-related factors. A similar study conducted by Kim et al. [13] in Korea demonstrated that subjects with uterine fibroids had an increased risk of thyroid nodules compared to that in subjects without uterine fibroids, especially among premenopausal women (43% vs. 27.8%). Multivariate logistic regression analysis showed that uterine fibroids were an independent factor that played a role in the occurrence of thyroid nodules. Additionally, Kim et al. further investigated the correlation between fibroids and the multiplicity and pathological types of thyroid nodules and showed that there was no relationship between the multiplicity of the thyroid nodules and the occurrence of uterine fibroids in the total, premenopausal, and postmenopausal subjects. According to the cytology or pathology results of the thyroid nodules, there was no significant difference in terms of the incidence of thyroid carcinoma between subjects with and without fibroids. Nonetheless, the situation in Chinese remains unclear to date. In this study, the association between thyroid nodules and fibroids was evaluated among 853 coastal Chinese reproductive-age women. The results showed that subjects with fibroids (65.28%) had a higher prevalence of thyroid nodules than those without uterine fibroids (52.73%). These findings were in accordance with previous studies; however, the prevalence of thyroid nodules in our study group was higher than that in Spinos’ and Kim’s groups [12, 13].

One possible explanation for this disparity was that the prevalence of thyroid nodules varies in areas with different iodine intake. Jiang et al. [21] determined the thyroid nodule prevalence in Beijing, which is an area of iodine deficiency. They found that the prevalence of thyroid nodules in Beijing was high, and it was higher in females (52.5%) than in males (42.7%). However, iodine intake has a dual role in the thyroid. Shan et al. [22] performed a cross-sectional study in 10 cities in China to understand the iodine status and thyroid disorder prevalence since the implementation of mandatory universal salt iodization for 16 years. A significant increase in thyroid nodules was noted compared with the results of their 5-year prospective study in 1999. In addition, the prevalence of thyroid nodules was significantly higher in MTAIII cities (median urine iodine concentration of 239.5 μg/L; including Xi’an, Nanjing, Wuhan, and Guiyang) than in ALL cities (median urine iodine concentration of 172.8 μg/L; including Shenyang, Beijing, Jinan, Chengdu, Shanghai, and Guangzhou), suggesting possible adverse effects of increased iodine intake. Similarly, Wenzhou is a coastal and iodine-sufficient city, and the government recommends the use of salt iodization. In addition, the different diagnostic criteria for thyroid nodules may also explain the different prevalence of thyroid nodules to some extent. Moreover, we also compared some ultrasonographic characteristics of thyroid nodules between subjects with and without uterine fibroids. Our findings indicated that a thyroid nodule size larger than 1 cm was more frequently observed in subjects with uterine fibroids than in subjects without uterine fibroids.

Although two previous studies have reported a relationship between uterine myoma and an increased risk of thyroid nodules [12, 13], we were unable to find any published literature about the association between thyroid nodules and fibroid-related factors. Therefore, we further compared several ultrasonographic characteristics of uterine fibroids between subjects with and without thyroid nodules. The results of our study showed that multiple fibroids were found more frequently in subjects with thyroid nodules than in subjects without thyroid nodules. Taken together, our study suggested a positive relationship between uterine fibroids and thyroid nodules in Chinese women.

Uterine fibroids are most prevalent during the reproductive period but are rarely observed before puberty; furthermore, they have a tendency to enlarge during pregnancy but to regress after menopause [23, 24]. Significantly increased estrogen receptor levels have been observed in uterine fibroid tissue compared with normal myometrial tissues [25, 26]. Factors that reduce the levels of endogenous estrogen may reduce the
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incidence of uterine fibroids [27]. Thus, it is now generally accepted that estrogen contributes to the development of uterine fibroids [3, 4, 24, 28]. To date, numerous studies have suggested that women are more likely to have thyroid nodules than men [6, 8]. Meanwhile, several previous studies have focused on the effects of estrogen to explain this gender difference. Furlanetto et al. [29] found that estradiol promoted the growth of rat FRTL-5 thyroid follicular cells in a time- and concentration-dependent manner. Manole et al. [30] demonstrated that 17β-estradiol stimulated the growth of benign and malignant thyroid tumor cells. Recently, Xu et al. [31] reported that estrogen promoted the proliferation and simultaneously inhibited the differentiation of thyroid stem and progenitor cells, which might become hypofunctioning or nonfunctioning thyroid nodule cells. Clinically, evidence indicates that pregnancy is related to the occurrence and development of thyroid nodules [32]; however, thyroid nodules grow slowly after menopause [33], suggesting that estrogen plays a significant role in the pathogenesis of thyroid nodules. Hence, combined with these findings, estrogen seems to be a common pathogenetic mechanism underlying the association between uterine fibroids and thyroid nodules.

Previous studies have indicated the association between uterine fibroids and thyroid hormone disorders; however, the results were inconsistent and inconclusive. In 1948, a case series by Rouhunkoski included 100 women with uterine fibroids and reported that there were 30 cases with nodular goiter, 29 cases with hyperthyroidism, and 12 cases with hypothyroidism, implying a high prevalence of thyroid disorders in women with uterine fibroids. Nevertheless, the limitation of the research was the absence of a control group [14]. In 1989, Lange and Meinen examined thyroid function among 79 women who had undergone hysterectomy for various reasons in Germany, and found that pathological TRH/TSH stimulation test results were more frequently seen in subjects with uterine fibroids than in those without fibroids, although the difference was not statistically significant [15]. In a recent study, Ott et al. [16] performed a retrospective study in Austria, and 215 sterile women (51 women with uterine fibroids and 164 unaffected controls) were included. They found that overt hypothyroidism was correlated with the presence of uterine fibroids, and women with overt hypothyroidism presented larger uterine fibroids. However, their conclusions were merely applicable to infertile women. These rather contradictory results in previous studies may be due to small numbers of participants, inclusion criteria and the lack of control. In addition to these discrepancies, there are no published studies regarding this association in Chinese to date. Hence, we investigated the correlation between thyroid function and uterine fibroids based on 853 reproductively women in China. In our study, regarding thyroid hormone levels, patients with uterine fibroids had significantly lower TT3 levels than unaffected controls; however, the TT3 levels were within the normal ranges. Additionally, no significant results were found with regard to the levels of TT4, FT3, FT4, or TSH between subjects with and without uterine fibroids. In addition, we conducted further research to explore the association between fibroids and different thyroid hormone statuses. However, no significant difference was noted in thyroid hormone status between subjects with and without uterine fibroids. Based on our findings, we speculate that uterine fibroids did not exhibit any correlation with the thyroid function evaluation index.

The present investigation should be acknowledged with some limitations. First, as a retrospective single-center analysis, the absence of data on the estrogen levels and thyroid autoimmunity status (anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) levels) for participating women is the main limitation. Second, iodine status, which was identified as the most frequent risk factor contributing to the development of thyroid nodules [34], was not evaluated in this study, although Wenzhou was a coastal and iodine-sufficient city. Other possible risk factors for the formation of thyroid nodules and uterine fibroids, such as tobacco smoking, alcohol consumption, and waist circumference, were not collected [35-39]. Third, there was a lack of cytological and/or histopathological results of thyroid nodules and uterine fibroids; thus, it was not possible to classify these masses as benign or malignant. Future multicenter studies that include pathological results and focus on the levels of estrogen, anti-TPO, and anti-TG; the iodine status; and other factors possibly related to thyroid nodules and uterine fibroids should be investigated to provide a more accurate and thorough assessment of the relationship.

In summary, our results indicated that patients with uterine fibroids had a significantly higher prevalence of thyroid nodules than patients without fibroids, suggesting that thyroid nodules are positively associated with uterine fibroids in Chinese individuals. Further studies are needed to confirm this association and fully understand the common pathogenetic mechanism underlying the association between uterine fibroids and thyroid nodules. Furthermore, the correlation between uterine fibroids and thyroid cancer will be the focus of our future research.

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Disclosure

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References

1. Stewart EA (2001) Uterine fibroids. Lancet 357: 293–298.
2. Vilos GA, Allaire C, Laberge PY, Leyland N (2015) The management of uterine leiomyomas. J Obstet Gynaecol Can 37: 157–178.
3. Hunter DS, Hodges LC, Eagon PK, Vonier PM, Fuchs-Youn g et al. (2000) Influence of exogenous estrogen receptor ligands on uterine leiomyoma: evidence from an in vitro animal model for uterine fibroids. Environ Health Perspect 108 Suppl 5: 829–834.
4. Yu L, Moore AB, Dixon D (2010) Receptor tyrosine kinases and their hormonal regulation in uterine leiomyoma. Semin Reprod Med 28: 250–259.
5. Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, et al. (2018) The diagnosis and management of thyroid nodules: a review. JAMA 319: 914–924.
6. Hegedus L (2004) Clinical practice. The thyroid nodule. N Engl J Med 351: 1764–1771.
7. Ezzat S, Sarti DA, Cain DR, Braunstein GD (1994) Thyroid incidentalomas. Prevalence by palpation and ultrasound. Arch Intern Med 154: 1838–1840.
8. Fan L, Tan L, Chen Y, Du C, Zhu M, et al. (2016) Metformin decreases thyroid volume and nodule size in subjects with insulin resistance: a preliminary study. Med Princ Pract 25: 233–236.
9. Anil K, Srinivasan M, Nar A, Bascil Tutuncu N, et al. (2016) Vitamin D and the risk of uterine fibroids. Epidemiology 24: 447–453.
10. American Thyroid Association (ATA) Guidelines Task-force on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, et al. (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19: 1167–1214.
11. Wang H, et al. (2016) The prevalence of thyroid nodules and an analysis of related lifestyle factors in Beijing communities. Int J Environ Res Public Health 13: 442.
12. Wang H, et al. (2016) Estrogen receptors and signaling in Fibroids: role in pathobiology and therapeutic implications. Reprod Sci 24: 1235–1244.
13. Reinhart MR, Mas A, Adam S, Kilic GS, et al. (2017) Estrogen receptors and signaling in Fibroids: role in pathobiology and therapeutic implications. Reprod Sci 24: 1235–1244.
14. Borahay MA, Asoglu MR, Mas A, Adam S, Kilic GS, et al. (2017) Estrogen receptors and signaling in Fibroids: role in pathobiology and therapeutic implications. Reprod Sci 24: 1235–1244.
15. Weinhagen P, et al. (2016) Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. Thyroid 26: 1125–1130.
16. Baumgartner MR, et al. (2017) Estrogen receptors and signaling in Fibroids: role in pathobiology and therapeutic implications. Reprod Sci 24: 1235–1244.
17. Weinhagen P, et al. (2016) Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. Thyroid 26: 1125–1130.
18. Borahay MA, Asoglu MR, Mas A, Adam S, Kilic GS, et al. (2017) Estrogen receptors and signaling in Fibroids: role in pathobiology and therapeutic implications. Reprod Sci 24: 1235–1244.
19. Weinhagen P, et al. (2016) Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. Thyroid 26: 1125–1130.
uterine leiomyoma: the role of hormonal modulation. *Semin Reprod Med* 22: 105–111.

28. Flake GP, Andersen J, Dixon D (2003) Etiology and pathogenesis of uterine leiomyomas: a review. *Environ Health Perspect* 111: 1037–1054.

29. Furlanetto TW, Nguyen LQ, Jameson JL (1999) Estradiol increases proliferation and down-regulates the sodium/iodide symporter gene in FRTL-5 cells. *Endocrinology* 140: 5705–5711.

30. Manole D, Schildknecht B, Gosnell B, Adams E, Derwahl M (2001) Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. *J Clin Endocrinol Metab* 86: 1072–1077.

31. Xu S, Chen G, Peng W, Renko K, Derwahl M (2013) Oestrogen action on thyroid progenitor cells: relevant for the pathogenesis of thyroid nodules? *J Endocrinol* 218: 125–133.

32. Kung AW, Chau MT, Lao TT, Tam SC, Low LC (2002) The effect of pregnancy on thyroid nodule formation. *J Clin Endocrinol Metab* 87: 1010–1014.

33. Costante G, Crocetti U, Schifino E, Ludovico O, Capula C, *et al.* (2004) Slow growth of benign thyroid nodules after menopause: no need for long-term thyroxine suppressive therapy in post-menopausal women. *J Endocrinol Invest* 27: 31–36.

34. Laurberg P, Jorgensen T, Perrild H, Ovesen L, Knudsen N, *et al.* (2006) The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol* 155: 219–228.

35. Knudsen N, Laurberg P, Perrild H, Bülow I, Ovesen L, *et al.* (2002) Risk factors for goiter and thyroid nodules. *Thyroid* 12: 879–888.

36. Rendina D, De Filippo G, Mossetti G, Zampa G, Muscariello R, *et al.* (2012) Relationship between metabolic syndrome and multinodular non-toxic goiter in an inpatient population from a geographic area with moderate iodine deficiency. *J Endocrinol Invest* 35: 407–412.

37. Yin J, Wang C, Shao Q, Qu D, Song Z, *et al.* (2014) Relationship between the prevalence of thyroid nodules and metabolic syndrome in the iodine-adequate area of Hangzhou, China: a cross-sectional and cohort study. *Int J Endocrinol* 2014: 675796.

38. Laughlin SK, Schroeder JC, Baird DD (2010) New directions in the epidemiology of uterine fibroids. *Semin Reprod Med* 28: 204–217.

39. Sparic R, Mirkovic L, Malvasi A, Tinelli A (2016) Epidemiology of uterine myomas: a review. *Int J Fertil Steril* 9: 424–435.