Impact of maternal thyroid hormone in late pregnancy on adverse birth outcomes: A retrospective cohort study in China

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Abstract. The purpose of this study was to explore the impact of maternal thyroid hormone dysfunction in late pregnancy on birth outcomes in a Chinese population. We retrospectively examined hospitalisation records and laboratory data between April 2016 and March 2017 and obtained results from 11,564 consecutive pregnant women with singleton births in which serum thyroid hormone had been examined together with birth outcomes. We assessed the association between maternal thyroid level and dysfunction with adverse birth outcomes based on regression analysis. Hyperthyroidism was associated with an increased risk of preterm birth (PTB, adjusted OR: 2.41, 95% CI: 1.83–3.17) and hypothyroidism was associated with an increased risk of small for gestational age (SGA, adjusted OR: 1.56, 95% CI: 1.10–2.22), while hyperthyroxinaemia was associated with a decreased risk of large for gestational age (LGA, adjusted OR: 0.64, 95% CI: 0.45–0.90). In addition, compared to women with normal FT3 and TSH (≥the 5th and ≤the 95th percentiles), women with high free triiodothyronine (FT3 >the 95th percentile) and low thyroid-stimulating hormone (TSH <the 95th percentile) had a 4.02-fold higher risk of PTB (95% CI: 2.05–7.88), and women with low FT3 and high TSH had a 4.22-fold greater risk of SGA (95% CI: 1.59–11.23). Our study supports associations between multiple types of maternal thyroid dysfunction in late pregnancy and adverse birth outcomes.

Key words: Thyroid hormones, Birth outcomes, Preterm birth, Small for gestational age, Large for gestational age

HEALTH SERVICES for women and children are provided through a three-tier system in China, which is composed of community, district, and city facilities. The central focus of tiered health care is on adverse birth outcomes, including preterm birth (PTB), low birthweight (LBW), and small for gestational age (SGA). PTB and fetal growth restriction (FGR) are the leading causes of perinatal mortality and morbidity. In addition, newborn infants diagnosed with PTB or small for gestational age (SGA) have an increased risk for morbidity, retarded growth, and disability in childhood, as well as for hypertension, type 2 diabetes mellitus, and cardiovascular disease in adulthood [1].

Thyroid hormones are essential for fetal growth and development [2]. Since fetal thyroid gland does not functionally mature until 20 weeks of gestation, the fetal requirement for thyroid hormones is dependent on maternal supply in the first half of pregnancy [3]. Various studies have shown that maternal thyroid dysfunction in the first or second trimester of pregnancy is associated with many adverse birth outcomes, such as PTB, SGA, and LBW [4-18]. Maternal thyroid function in late pregnancy is closely associated with fetal thyroid status contributing to the utilisation of fetal thyroid hormones [19, 20]. However, few studies have investigated maternal thyroid function in late pregnancy and have yielded conflicting results [21-24]. For example, Phoojaroenchanachai et al. and Luewan et al. showed that maternal hyperthyroidism in late pregnancy is associated with an increased risk of PTB, FGR, and LBW [21, 22]. In contrast, the results of Idris et al. and Männistö et al. indicated that maternal...
hypothyroidism in the third trimester of pregnancy may increase the risk of LBW and PTB [23, 24]. In addition, longitudinal studies have investigated maternal thyroid function during pregnancy and suggested that the relationship between maternal thyroid dysfunction and adverse birth outcomes vary with trimester [25-27]. However, none of these studies investigated all types of thyroid disorders in late pregnancy and their effects on adverse birth outcomes. In addition, in most studies of thyroid hormones during pregnancy, free thyroxin (FT4) and thyroid-stimulating hormone (TSH) levels were investigated. There is a considerable gap in our understanding of the association between other thyroid hormones such as free triiodothyronine (FT3) and birth outcomes in late pregnancy.

We conducted an observational hospital-based cohort study in Changzhou city, Jiangsu province, China to investigate the relationship between multiple types of maternal thyroid dysfunction in late pregnancy and unfavourable birth outcomes. We hypothesised that a combined higher or lower level of multiple thyroid hormones in late pregnancy would have a more pronounced effect on these outcomes (i.e. PTB and SGA) than when only one hormone was abnormal.

Materials and Methods

Study population and data collection

This observational hospital-based cohort study was performed in the city of Changzhou in China, an iodine-sufficient area. Between April 2016 and March 2017, pregnant women presenting for delivery in Changzhou Maternity and Child Health Care Hospital Affiliated with Nanjing Medical University were enrolled in this study. The study design was approved by the ethics committee of the hospital (no. ZD201803). Informed consent in this study was not required because of anonymous data. Women were included in this cohort study if they had a singleton pregnancy and women were excluded if they had a history of pre-gestational illnesses that could affect thyroid function and birth outcomes, including thyroid disorders, diabetes mellitus (type 1 or 2), chronic hypertension, chronic heart, liver and kidney diseases, immune rheumatic disease, and syphilis; or had a medical abortion, intrauterine fetal death, or fetus with congenital malformations; or had no tests of thyroid hormones upon hospital admission. Pregnancy outcomes and the levels of maternal thyroid hormones were downloaded from the hospital records and laboratory information system, respectively. No data were provided on whether the participants had received medication for thyroid dysfunction during pregnancy. The influence of thyroid hormone levels caused by the medication was not excluded, which may contribute to the bias. Blood samples were taken at the time of admission for delivery. High-risk pregnant women might be admitted to the hospital earlier, so that blood samples were taken in earlier gestational weeks than others, which may affect the result. Serum FT3, FT4, TSH, and thyroid peroxidase antibody (TPO-Ab) were determined based on electrochemiluminescence immunoassays using a Cobas E1201 platform (Roche Diagnostics, Switzerland). The detection limits were 0.4–50 pmol/L for FT3, 0.3–100 pmol/L for FT4, 0.01–100 mIU/L for TSH, and 5–600 IU/mL for TPO-Ab. According to the manufacturer’s instructions, the normal references of FT3, FT4, TSH, and TPOAb were 3.1–6.8 pmol/L, 12–22 pmol/L, 0.27–4.2 mIU/L, and 3±34 IU/mL, respectively.

Definition of maternal and fetal outcomes

Gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy (ICP), pre-eclampsia (PE), and pregnancy induced hypertension (PIH) were considered as major pregnancy complications and PTB, SGA, and large for gestational age (LGA) as adverse birth outcomes. The diagnosis of pregnancy complications was based on previous reports [28]. Deliveries prior to 37 weeks of gestation were defined as PTB [29]. According to the Chinese reference curve on birth weight reported in a previous cohort study, the neonates were classified into three groups: (1) SGA, birth weights were <the 10th percentile at gestational week-specific levels; (2) appropriate for gestational age (AGA), birth weights between the 10th and 90th percentiles; (3) LGA, birth weights greater than the 90th percentile [30].

Statistical analysis

Demographic characteristics of this study were expressed as means ± standard deviation (SD) for normally distributed continuous variables, medians (inter-quartile range [IQR]) for continuous variables with skewed distribution, and N (%) for categorical variables. Parametric and non-parametric methods were used to compare the differences in demographic characteristics between the AGA and SGA/LGA mother–neonate pairs. When gestational age, birth length, and birth weight were treated as continuous variables, general linear models were applied to assess the association between different indexes of thyroid function (FT3, FT4, TSH, and TPO-Ab positivity) and these variables. After the adverse birth outcomes were defined as categorical variables (PTB/SGA/LGA), logistic regression models were applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the effect of thyroid hormones (FT3, FT4, and TSH). The models were adjusted for the following covariates: Maternal age, gravity,
Thyroid hormone and birth outcomes

Results

Population characteristics

All participants with multiple gestation, congenital malformations of newborns, medical abortion, adverse pre-gestational disease such as pre-existing thyroid disease, and lack of thyroid hormone levels were excluded from the present study (n = 1,711). A total of 11,564 mother-and-singleton-newborn pairs were included in the final analysis. Most maternal blood samples were tested at the corresponding gestational weeks at delivery (median gestational age: 39 weeks; minimum: 28 weeks; maximum: 41 weeks). Maternal and neonatal baseline characteristics in this study are shown in Table 1 and Table 2. Mean maternal age and BMI at delivery was 28.6 ± 4.4 years old and 27.33 ± 3.37 kg/m², respectively. More than 60% of women were nulliparous. The incidence of maternal GDM, ICP, PE, PIH, delivery mode, neonatal sex, and TPO-Ab positivity. Based on the percentile distribution of thyroid hormone levels in women with TPO-Ab negativity, maternal thyroid function was defined as: Euthyroid, normal FT4 and TSH (≥5th and ≤95th percentiles); hypothyroxinaemia, low FT4 (<the 5th percentile) and normal TSH; hypothyroidism, high TSH (>the 95th percentile) and normal FT4 or low FT4; hyperthyroxinaemia, high FT4 and normal TSH; and hyperthyroidism, low TSH and normal FT4 or high FT4 [31, 32]. TPO-Ab >34.0 mIU/L was considered positive according to the manufacturer’s instructions. All data analyses were performed using the EmpowerStats software (X&Y solutions inc., USA) and R (version 3.4.2, http://www.R-project.org). A p-value of <0.05 was considered to indicate statistical significance.

Maternal serum levels of thyroid hormones and fetal growth

The reference intervals for FT3, FT4, and TSH according to the 5th and 95th percentiles of subjects with TPO-Ab negativity were 3.19–4.98 pmol/L, 9.84–15.97 pmol/L, and 0.99–6.29 mIU/L, respectively. The association between maternal thyroid hormone levels in late pregnancy and gestational age, birth length, and weight are shown in Table 3. We found that a 1 mIU/L increase in TSH levels in late pregnancy was associated with a 11.71 g decrease in birth weight (95% CI: –16.85, –6.58) in crude linear regression models; these associations remained significant after adjusting for potential confounding factors (β: –5.47, 95% CI: –9.39, –1.55). The adjusted models showed that maternal serum FT3 and FT4 levels were inversely associated with gestational age. In addition, we found that FT4 decreased the birth weight in the crude models (β: –23.53, 95% CI: –28.27, –18.80), but the decrease did not remain significant in the adjusted models (β: –3.63, 95% CI: –7.34, –0.08, p = 0.055).

Maternal thyroid hormone dysfunction and adverse birth outcomes

Associations of maternal thyroid dysfunction with risk for adverse birth outcomes in unadjusted and adjusted logistic regression models are shown in Table 4. Hyperthyroidism was associated with increased PTB; the adjusted OR (95% CI) was 2.41 (1.83–3.17). Hypothyroidism was associated with increased SGA; the adjusted OR (95% CI) was 1.56 (1.10–2.22). Hyperthyroxinaemia was associated with decreased LGA (adjusted OR: 0.65, 95% CI: 0.46–0.92). No significant associations of hypothyroxinaemia with PTB, SGA, and LGA were observed in adjusted logistic regression models. In addition, the relationship between each thyroid hormone level and adverse birth outcomes are also shown in Table 5. Maternal serum FT3 level in late pregnancy was positively associated with the risk for PTB and SGA after adjusting for potential confounders (PTB: adjusted OR: 1.35, 95% CI: 1.21–1.52; SGA: adjusted OR: 1.13, 95% CI: 1.01–1.26). A positive association between TSH level and SGA risk was observed in the adjusted models, whereas
associations between thyroid hormone and LGA were null. High FT3 or high TSH (>95th percentile) was associated with an increased risk of SGA (adjusted OR: 1.54, 95% CI: 1.15–2.06 or adjusted OR: 1.53, 95% CI: 1.18–1.99). Compared to women with normal FT3, the PTB risk in those with high FT3 significantly increased by 1.58-fold (95% CI: 1.17–2.14). Women with low TSH had a 2.36-fold higher risk of PTB when compared to those with normal TSH (95% CI: 1.80–3.09). When compared to normal FT4, high FT4 levels were associated with an increased risk of PTB (adjusted OR: 1.37, 95% CI: 1.01–1.86) and with a decreased risk of LGA

Table 1 Descriptive statistics [median (IQR) or mean ± SD or N (%) ] for maternal and neonatal characteristics in the study population (N = 11,564)

| Characteristics                  | Total (N = 11,564) | SGA (N = 1,023) | AGA (N = 8,750) | LGA (N = 1,791) | p     |
|----------------------------------|-------------------|----------------|----------------|----------------|-------|
| Age at delivery (years)          |                   |                |                |                |       |
| <35                              | 28.60 ± 4.42      | 27.84 ± 4.38   | 28.43 ± 4.32   | 29.90 ± 4.68   | <0.001|
| ≥35                              | 10,242 (88.57%)   | 931 (91.01%)   | 7,842 (89.62%) | 1,469 (82.02%) | <0.001|
| BMI at delivery (kg/m²)          |                   |                |                |                |       |
| <25                              | 27.33 ± 3.37      | 25.78 ± 3.26   | 27.15 ± 3.23   | 29.08 ± 3.44   | <0.001|
| ≥25                              | 2,856 (24.95%)    | 442 (43.89%)   | 2,236 (25.80%) | 178 (10.02%)   | <0.001|
| Gravidity                        |                   |                |                |                |       |
| <3                               | 8,219 (71.07%)    | 791 (77.32%)   | 6,350 (72.57%) | 1,078 (60.19%) | <0.001|
| ≥3                               | 3,345 (28.93%)    | 232 (22.68%)   | 2,400 (27.43%) | 713 (39.81%)   |       |
| Parity                           |                   |                |                |                |       |
| No child                         | 6,945 (60.06%)    | 702 (68.62%)   | 5,418 (61.92%) | 473 (6.25%)    | <0.001|
| ≥1 child                         | 4,619 (39.94%)    | 321 (31.38%)   | 3,332 (38.08%) | 666 (53.94%)   | <0.001|
| Gestational age at delivery (week)|                   |                |                |                |       |
| <25                              | 38.69 ± 1.67      | 38.61 ± 2.22   | 38.76 ± 1.60   | 38.40 ± 1.60   | <0.001|
| ≥25                              | 120.98 ± 12.03    | 123.22 ± 15.03 | 120.67 ± 11.63 | 121.19 ± 11.89 | <0.001|
| Systolic BP at delivery (mmHg)   |                   |                |                |                |       |
| <25                              | 74.52 ± 8.26      | 76.50 ± 9.97   | 74.33 ± 8.04   | 74.28 ± 8.13   | <0.001|
| ≥25                              | 6,649 (57.50%)    | 680 (66.47%)   | 5,239 (59.87%) | 730 (40.76%)   | <0.001|
| Cesarean section                 |                   |                |                |                |       |
| No child                         | 4,915 (42.50%)    | 343 (33.53%)   | 3,511 (40.13%) | 1,061 (59.24%) | <0.001|
| ≥1 child                         | 793 (6.86%)       | 124 (12.12%)   | 541 (61.8%)    | 128 (7.15%)    | <0.001|
| PTB                              | 969 (8.38%)       | 54 (5.28%)     | 643 (7.35%)    | 272 (15.19%)   | <0.001|
| GDM                              | 715 (6.18%)       | 77 (7.53%)     | 525 (6.00%)    | 113 (6.31%)    | 0.04  |
| ICP                              | 396 (3.42%)       | 99 (9.68%)     | 235 (2.69%)    | 62 (3.46%)     | <0.001|
| PIH                              | 246 (2.13%)       | 22 (2.15%)     | 174 (1.99%)    | 50 (2.79%)     | 0.022 |
| Delivery mode                    |                   |                |                |                |       |
| Vaginal delivery                 |                   |                |                |                |       |
| Cesarean section                 |                   |                |                |                |       |
| No child                         | 648 (5.60%)       | 63 (6.16%)     | 473 (5.41%)    | 112 (6.25%)    | 0.263 |
| ≥1 child                         | 4.05 ± 0.58       | 4.06 ± 0.61    | 4.05 ± 0.58    | 4.07 ± 0.56    | 0.76  |
| Fetal sex                        |                   |                |                |                |       |
| Female                           | 12.75 ± 1.90      | 13.05 ± 2.06   | 12.77 ± 1.89   | 12.43 ± 1.82   | <0.001|
| Male                             | 2.65 (1.85–3.79)  | 2.82 (1.90–4.18) | 2.67 (1.85–3.78) | 2.53 (1.80–3.64) | <0.001|
| TPO-Ab positivity                |                   |                |                |                |       |
| FT3 (pmol/L)                     | 5.451 (47.14%)    | 618 (60.41%)   | 4,182 (47.79%) | 651 (36.35%)   | <0.001|
| FT4 (pmol/L)                     | 6,113 (52.86%)    | 405 (39.59%)   | 4,568 (52.21%) | 1,140 (63.65%) | <0.001|
| TSH (mIU/L)                      | 49.81 ± 1.43      | 48.61 ± 2.94   | 49.83 ± 1.05   | 50.42 ± 1.28   | <0.001|
| Fetal birth height (cm)          | 3,342.17 ± 496.77 | 2,619.76 ± 413.79 | 3,305.28 ± 369.17 | 3,935.04 ± 416.71 | <0.001|

P values were derived from comparisons among the characteristics of SGA, AGA and LGA neonates. IQR, interquartile range; SD, standard deviation; SGA/AGA/LGA, small/appropriate/large for gestational age; BMI, body mass index; BP, blood pressure; PTB, preterm birth; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; TPO-Ab, thyroid peroxidase antibody; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.
Table 2  Descriptive statistics [median (IQR) or mean ± SD or N (%)] for maternal and neonatal characteristics in the study population according to maternal thyroid function (N = 11,517)*

| Characteristics                      | Euthyroid (N = 9,371) | Hypothyroxinaemia (N = 528) | Hypothyroidism (N = 557) | Hyperthyroxinaemia (N = 505) | Hyperthyroidism (N = 552) | p     |
|--------------------------------------|-----------------------|-----------------------------|--------------------------|-----------------------------|---------------------------|-------|
| Age at delivery (years)              |                       |                             |                          |                             |                           |       |
| <35                                  | 28.63 ± 4.40          | 29.64 ± 4.66                | 27.81 ± 4.21             | 27.37 ± 4.32                | 29.13 ± 4.50              | <0.001|
| ≥35                                  | 8,303 (88.60%)        | 431 (81.63%)                | 510 (91.56%)             | 474 (93.86%)                | 477 (86.41%)              | <0.001|
| BMI at delivery (kg/m²)              | 27.35 ± 3.34          | 29.23 ± 3.17                | 26.84 ± 3.18             | 25.52 ± 3.38                | 27.33 ± 3.30              | <0.001|
| <25                                  | 2,271 (24.45%)        | 27 (5.20%)                  | 149 (27.24%)             | 255 (51.20%)                | 135 (24.77%)              | <0.001|
| ≥25                                  | 7,017 (75.55%)        | 492 (94.80%)                | 398 (72.76%)             | 243 (48.80%)                | 410 (75.23%)              |       |
| Gravidity                            |                       |                             |                          |                             |                           |       |
| <3                                   | 6,659 (71.06%)        | 340 (64.39%)                | 423 (75.94%)             | 389 (77.03%)                | 369 (66.85%)              | <0.001|
| ≥3                                   | 2,712 (28.94%)        | 188 (35.61%)                | 134 (24.06%)             | 116 (22.97%)                | 183 (33.15%)              |       |
| Parity                               |                       |                             |                          |                             |                           |       |
| No child                             | 5,587 (59.62%)        | 309 (58.52%)                | 397 (71.27%)             | 334 (66.14%)                | 284 (51.45%)              | <0.001|
| ≥1 child                             | 3,784 (40.38%)        | 219 (41.48%)                | 160 (28.73%)             | 171 (33.86%)                | 268 (48.55%)              |       |
| Gestational age at delivery (week)   | 38.73 ± 1.65          | 38.64 ± 1.84                | 38.66 ± 1.56             | 38.61 ± 1.51                | 38.24 ± 1.99              | <0.001|
| Systolic BP at delivery (mmHg)       | 120.88 ± 11.97        | 122.83 ± 13.71              | 122.87 ± 12.59           | 119.67 ± 11.30              | 120.06 ± 10.92            | <0.001|
| Diastolic BP at delivery (mmHg)      | 74.44 ± 8.20          | 75.30 ± 9.47                | 76.01 ± 8.36             | 74.24 ± 8.37                | 73.65 ± 7.40              | <0.001|
| Delivery mode                        |                       |                             |                          |                             |                           |       |
| Vaginal delivery                     | 5,390 (57.52%)        | 254 (48.11%)                | 396 (71.10%)             | 336 (66.53%)                | 240 (43.48%)              | <0.001|
| Cesarean section                     | 3,981 (42.48%)        | 274 (51.89%)                | 161 (28.90%)             | 169 (33.47%)                | 312 (56.52%)              |       |
| PTB                                  | 592 (6.32%)           | 46 (8.71%)                  | 40 (7.18%)               | 40 (7.92%)                  | 70 (12.68%)               | <0.001|
| GDM                                  | 771 (8.23%)           | 54 (10.23%)                 | 49 (8.80%)               | 30 (5.94%)                  | 61 (11.05%)               | 0.010 |
| ICP                                  | 563 (6.01%)           | 35 (6.63%)                  | 55 (9.87%)               | 32 (6.34%)                  | 26 (5.45%)                | 0.009 |
| PE                                   | 291 (3.11%)           | 46 (8.71%)                  | 29 (5.21%)               | 14 (2.77%)                  | 12 (2.17%)                | <0.001|
| PIH                                  | 201 (2.14%)           | 16 (3.03%)                  | 18 (3.23%)               | 4 (0.79%)                   | 7 (1.27%)                 | 0.047 |
| Characteristics | Euthyroid (N = 9,371) | Hypothyroxinaemia (N = 528) | Hypothyroidism (N = 557) | Hyperthyroxinaemia (N = 505) | Hyperthyroidism (N = 552) | p  |
|-----------------|-----------------------|-----------------------------|--------------------------|----------------------------|--------------------------|----|
| Thyroid hormones |                       |                             |                          |                            |                          |    |
| TPO-Ab positivity | 502 (5.36%)           | 35 (6.63%)                  | 40 (7.18%)               | 29 (5.74%)                 | 40 (7.25%)               | 0.169 |
| FT3 (pmol/L)     | 4.04 ± 0.55           | 4.00 ± 0.54                 | 4.16 ± 0.56              | 4.15 ± 0.62                | 4.19 ± 0.96              | <0.001 |
| FT4 (pmol/L)     | 12.68 ± 1.46          | 9.21 ± 0.55                 | 12.53 ± 1.70             | 17.03 ± 0.99               | 13.39 ± 2.17             | <0.001 |
| TSH (mIU/L)      | 2.64 (1.92–3.63)      | 2.75 (2.00–3.64)            | 7.41 (6.77–8.60)         | 2.72 (1.91–3.75)           | 0.74 (0.50–0.89)         | <0.001 |
| Fetal sex        |                       |                             |                          |                            |                          |    |
| Female           | 4,400 (46.95%)        | 247 (46.78%)                | 246 (44.17%)             | 229 (45.35%)               | 309 (55.98%)             | 0.001 |
| Male             | 4,971 (53.05%)        | 281 (53.22%)                | 311 (55.83%)             | 276 (54.65%)               | 243 (44.02%)             |    |
| Fetal birth height (cm) | 49.83 ± 1.41  | 49.84 ± 1.60            | 49.76 ± 1.50             | 49.80 ± 1.25               | 49.65 ± 1.68             | 0.006 |
| Fetal birth weight (gram) | 3,352.23 ± 49.15 | 3,395.46 ± 550.25       | 3,257.29 ± 507.45        | 3,241.00 ± 446.88          | 3,301.13 ± 540.01        | <0.001 |
| <2,500           | 397 (42.4%)           | 29 (5.49%)                  | 32 (5.75%)               | 17 (3.37%)                 | 39 (7.07%)               | <0.001 |
| 2,500–4,000      | 8,276 (88.32%)        | 442 (83.71%)                | 489 (87.79%)             | 472 (93.47%)               | 471 (85.33%)             |    |
| >4,000           | 698 (74.5%)           | 57 (10.80%)                 | 36 (6.46%)               | 16 (3.17%)                 | 42 (7.61%)               |    |
| Weight for gestational age | SGA       | 802 (85.6%)                | 41 (7.77%)               | 79 (14.18%)                | 64 (12.67%)              | 35 (63.4%) |
| AGA             | 7,111 (75.88%)        | 378 (71.59%)                | 406 (72.89%)             | 400 (79.21%)               | 414 (75.00%)             | <0.001 |
| LGA             | 1,458 (15.56%)        | 109 (20.64%)                | 72 (12.93%)              | 41 (8.12%)                 | 103 (18.66%)             |    |

*Excluding 23 cases with FT4 < the 5th and TSH < the 5th percentile and 28 cases with FT4 > the 95th and TSH > the 95th percentile.

IQR, interquartile range; SD, standard deviation; BMI, body mass index; BP, blood pressure; PTB, preterm birth; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; TPO-Ab, thyroid peroxidase antibody; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; SGA/AGA/LGA small/appropriate/large for gestational age.
In addition, FT4 levels were significantly associated with a decreased risk of PE (adjusted OR: 0.93, 95% CI: 0.88–0.99, \( p = 0.015 \)), but not with other pregnancy complications and adverse birth outcomes after adjusting for maternal age and BMI. Maternal thyroid TPO-Ab positivity in late pregnancy was not associated with the risks of PTB, SGA, and LGA. For the combined effect of FT3 and TSH on PTB and SGA, when compared to women with normal TSH and FT3 (≥the 5th and ≤the 95th percentiles), the risk of PTB was remarkably significantly higher among those with high FT3 and low TSH (adjusted OR: 4.02, 95% CI: 2.05–7.88, \( p < 0.001 \)), and the risk of SGA was remarkably significantly higher among those with low FT3 and high TSH (adjusted OR, 4.22, 95% CI: 1.59–11.23, \( p = 0.004 \), Table 6).

### Table 3  Association between maternal thyroid hormone levels in late pregnancy and fetal development in unadjusted and adjusted models

|                        | Gestational age (weeks)\(^a\) | Birth length (cm)\(^b\) | Birth weight (g)\(^b\) |
|------------------------|-------------------------------|-------------------------|------------------------|
|                        | \( \beta \) (95%CI) | \( p \) | \( \beta \) (95%CI) | \( p \) | \( \beta \) (95%CI) | \( p \) |
| **Unadjusted**          |                               |                          |                        |
| FT3 (pmol/L)            | –0.12 (–0.17, –0.07)          | <0.001                  | –0.06 (–0.10, –0.01)   | 0.011 | –9.88 (–25.44, 5.69) | 0.214 |
| FT4 (pmol/L)            | –0.02 (–0.04, –0.01)          | 0.005                   | –0.02 (–0.03, –0.00)   | 0.018 | –23.53 (–28.27, –18.80) | <0.001 |
| TSH (mIU/L)             | 0.01 (–0.01, 0.03)            | 0.180                   | –0.01 (–0.02, 0.01)    | 0.302 | –11.71 (–16.85, –6.58) | <0.001 |
| TPO-Ab positives        | –0.20 (–0.33, –0.07)          | 0.003                   | –0.09 (–0.20, 0.03)    | 0.131 | –35.90 (–75.27, 3.46) | 0.0739 |
| **Adjusted**            |                               |                          |                        |
| FT3 (pmol/L)            | –0.20 (–0.25, –0.15)          | <0.001                  | –0.01 (–0.04, 0.02)    | 0.638 | –9.78 (–21.71, 2.14) | 0.108 |
| FT4 (pmol/L)            | –0.02 (–0.04, –0.01)          | 0.003                   | –0.00 (–0.01, 0.00)    | 0.362 | –3.63 (–7.34, 0.08)  | 0.055 |
| TSH (mIU/L)             | 0.00 (–0.01, 0.02)            | 0.824                   | –0.01 (–0.02, 0.00)    | 0.163 | –5.47 (–9.39, –1.55) | 0.006 |
| TPO-Ab positives        | –0.12 (–0.24, 0.01)           | 0.072                   | 0.04 (–0.03, 0.11)     | 0.295 | –4.93 (–34.30, 24.44) | 0.742 |

\( ^a \) Adjusted for maternal age, gravidity, parity, BMI, systolic and diastolic BP at delivery, GDM, ICP, PE, PIH, delivery mode and neonatal sex. \( ^b \) Additionally corrected for gestational age.

FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TPO-Ab, thyroid peroxidase antibody; BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension.

### Table 4  Associations between multiple types of maternal thyroid dysfunction late pregnancy and different adverse birth outcomes in unadjusted and adjusted models

|                        | PTB\(^a\)  | SGA\(^b\)  | LGA\(^b\)  |
|------------------------|------------|------------|------------|
|                        | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| **Unadjusted**          |            |            |            |
| Euthyroid              |            |            |            |
| Hypothyroxinaemia      | 1.42 (1.03, 1.94) | 0.030 | 0.96 (0.69, 1.34) | 0.817 | 1.41 (1.13, 1.75) | 0.002 |
| Hypothyroidism         | 1.15 (0.82, 1.60) | 0.418 | 1.73 (1.34, 2.22) | <0.001 | 0.86 (0.67, 1.12) | 0.268 |
| Hyperthyroxinaemia     | 1.28 (0.91, 1.78) | 0.153 | 1.42 (1.08, 1.87) | 0.012 | 0.50 (0.36, 0.69) | <0.001 |
| Hyperthyroidism        | 2.15 (1.65, 2.80) | <0.001 | 0.75 (0.53, 1.07) | 0.109 | 1.21 (0.97, 1.52) | 0.089 |
| **Adjusted**            |            |            |            |
| Euthyroid              |            |            |            |
| Hypothyroxinaemia      | 1.24 (0.87, 1.75) | 0.232 | 0.80 (0.46, 1.39) | 0.419 | 1.03 (0.81, 1.31) | 0.795 |
| Hypothyroidism         | 1.05 (0.75, 1.48) | 0.776 | 1.56 (1.10, 2.22) | 0.013 | 1.04 (0.80, 1.37) | 0.753 |
| Hyperthyroxinaemia     | 1.14 (0.80, 1.63) | 0.453 | 1.13 (0.77, 1.66) | 0.519 | 0.65 (0.46, 0.92) | 0.014 |
| Hyperthyroidism        | 2.41 (1.83, 3.17) | <0.001 | 0.73 (0.44, 1.21) | 0.224 | 1.10 (0.87, 1.40) | 0.430 |

\( ^a \) Adjusted for maternal age, gravidity, parity, gestational age, BMI, systolic and diastolic BP at delivery, GDM, ICP, PE, PIH, delivery mode, neonatal sex and TPO-Ab positivity. \( ^b \) Additionally corrected for gestational age.

PTB, preterm birth; SGA/LGA, small/large for gestational age; BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; TPO-Ab, thyroid peroxidase antibody.

(adjusted OR: 0.67, 95% CI: 0.49, 0.92). In addition, FT4 levels were significantly associated with a decreased risk of PE (adjusted OR: 0.93, 95% CI: 0.88–0.99, \( p = 0.015 \)), but not with other pregnancy complications and adverse birth outcomes after adjusting for maternal age and BMI. Maternal thyroid TPO-Ab positivity in late pregnancy was not associated with the risks of PTB, SGA, and LGA. For the combined effect of FT3 and TSH on PTB and SGA, when compared to women with normal TSH and FT3 (≥the 5th and ≤the 95th percentiles), the risk of PTB was remarkably significantly higher among those with high FT3 and low TSH (adjusted OR: 4.02, 95% CI: 2.05–7.88, \( p < 0.001 \)), and the risk of SGA was remarkably significantly higher among those with low FT3 and high TSH (adjusted OR, 4.22, 95% CI: 1.59–11.23, \( p = 0.004 \), Table 6).
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Table 5  Associations between maternal thyroid hormone levels in late pregnancy and adverse birth outcomes in unadjusted and adjusted models

|                      | PTB   | SGA   | LGA   |
|----------------------|-------|-------|-------|
|                      | OR (95%CI) | p   | OR (95%CI) | p   | OR (95%CI) | p   |
| **Unadjusted**       |       |       |       |
| FT3 (pmol/L)         | 1.27 (1.14, 1.41) | <0.001 | 1.03 (0.92, 1.15) | 0.610 | 1.04 (0.95, 1.13) | 0.369 |
| FT4 (pmol/L)         | 1.01 (0.98, 1.05) | 0.468 | 1.08 (1.04, 1.11) | <0.001 | 0.91 (0.88, 0.93) | <0.001 |
| TSH (mIU/L)          | 0.99 (0.95, 1.03) | 0.675 | 1.09 (1.06, 1.13) | <0.001 | 0.96 (0.93, 0.99) | 0.010 |
| TPO-Ab positives     | 1.45 (1.10, 1.90) | 0.008 | 1.15 (0.88, 1.51) | 0.317 | 1.17 (0.94, 1.44) | 0.154 |
| FT3 5–95th percentile| Ref. |       | Ref. |       | Ref. |       |
| FT3 >95th percentile | 1.43 (1.07, 1.92) | 0.015 | 1.39 (1.06, 1.82) | 0.018 | 1.10 (0.87, 1.38) | 0.425 |
| FT3 <5th percentile  | 0.85 (0.59, 1.21) | 0.361 | 1.28 (0.97, 1.69) | 0.977 | 0.93 (0.73, 1.18) | 0.547 |
| FT4 5–95th percentile| Ref. |       | Ref. |       | Ref. |       |
| FT4 >95th percentile | 1.50 (1.12, 2.00) | 0.006 | 1.40 (1.08, 1.80) | 0.011 | 0.54 (0.40, 0.72) | <0.001 |
| FT4 <5th percentile  | 1.49 (1.11, 1.99) | 0.008 | 0.92 (0.67, 1.27) | 0.606 | 1.45 (1.17, 1.79) | <0.001 |
| TSH 5–95th percentile| Ref. |       | Ref. |       | Ref. |       |
| TSH >95th percentile | 1.13 (0.82, 1.56) | 0.460 | 1.68 (1.31, 2.15) | <0.001 | 0.87 (0.67, 1.11) | 0.263 |
| TSH <5th percentile  | 2.05 (1.58, 2.66) | <0.001 | 0.71 (0.50, 1.00) | 0.053 | 1.24 (1.00, 1.54) | 0.050 |
| **Adjusted**         |       |       |       |
| FT3 (pmol/L)         | 1.35 (1.21, 1.52) | <0.001 | 1.13 (1.01, 1.26) | 0.032 | 0.93 (0.85, 1.03) | 0.174 |
| FT4 (pmol/L)         | 1.01 (0.97, 1.05) | 0.797 | 1.02 (0.98, 1.05) | 0.414 | 0.97 (0.94, 1.00) | 0.059 |
| TSH (mIU/L)          | 0.96 (0.92, 1.00) | 0.075 | 1.06 (1.03, 1.10) | <0.001 | 1.01 (0.98, 1.04) | 0.583 |
| TPO-Ab positives     | 1.30 (0.97, 1.75) | 0.076 | 1.05 (0.79, 1.41) | 0.732 | 1.07 (0.85, 1.34) | 0.574 |
| FT3 5–95th percentile| Ref. |       | Ref. |       | Ref. |       |
| FT3 >95th percentile | 1.58 (1.17, 2.14) | 0.003 | 1.54 (1.15, 2.06) | 0.003 | 0.89 (0.69, 1.14) | 0.356 |
| FT3 <5th percentile  | 0.77 (0.53, 1.12) | 0.176 | 1.07 (0.80, 1.44) | 0.635 | 0.95 (0.73, 1.23) | 0.674 |
| FT4 5–95th percentile| Ref. |       | Ref. |       | Ref. |       |
| FT4 >95th percentile | 1.37 (1.01, 1.86) | 0.043 | 1.08 (0.82, 1.42) | 0.591 | 0.67 (0.49, 0.92) | 0.014 |
| FT4 <5th percentile  | 1.32 (0.96, 1.82) | 0.090 | 1.10 (0.78, 1.55) | 0.586 | 1.06 (0.85, 1.33) | 0.613 |
| TSH 5–95th percentile| Ref. |       | Ref. |       | Ref. |       |
| TSH >95th percentile | 1.06 (0.76, 1.48) | 0.731 | 1.53 (1.18, 1.99) | 0.001 | 1.06 (0.81, 1.39) | 0.652 |
| TSH <5th percentile  | 2.36 (1.80, 3.09) | <0.001 | 0.69 (0.48, 1.00) | 0.048 | 1.12 (0.89, 1.41) | 0.337 |

* Adjusted for maternal age, gravidity, parity, gestational age, BMI, systolic and diastolic BP at delivery, GDM, ICP, PE, PIH, delivery mode, neonatal sex and TPO-Ab positivity. ** Additionally corrected for gestational age.

PTB, preterm birth; SGA/LGA, small/large for gestational age; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; TPO-Ab, thyroid peroxidase antibody.

Discussion

There were several main findings from this large hospital-based cohort study of a Chinese population. First, when compared to euthyroid women, hypothyroxi-naemia women had a higher incidence of PE (8.71% vs. 3.11%, p < 0.001), hypothyroidism women had a higher incidence of ICP and PE (for ICP: 9.87% vs. 6.01%, for PE: 5.21% vs. 3.11%, all p < 0.001), and hyperthyroidism women had a higher incidence GDM (11.05% vs. 8.23%, p = 0.038) after adjusting for age and BMI. Second, pregnant women with hyperthyroidism had a 2.41-fold greater risk of PTB, those with hypothyroidism had a 1.56-fold increased risk of SGA, and those with hyperthyroxi-naemia had a 35% decreased risk of LGA. Third, SGA offspring were positively correlated with maternal serum TSH and FT3, but not with FT4. There was a significant positive correlation between maternal serum FT3 and PTB. Pregnant women with high FT3 and low TSH had a 4.02-fold increased risk of PTB, and those with low FT3 and high TSH and a 4.22-fold greater risk of SGA.

There have been several cohort studies evaluating the impact of thyroid dysfunction in pregnancy on PTB and/or birth weight in the past decade. Evidence from these studies suggest that maternal hypothyroidism (clinical and subclinical), isolated hypothyroxinemia, and TPO-Ab positivity are significantly associated with...
### Table 6 Combined effect of FT3 and TSH in late pregnancy on PTB and SGA

| Thyroid hormone levels | PTB | SGA | p |
|------------------------|-----|-----|---|
|                        | OR (95%CI) | OR (95%CI) | p |
| **unadjusted**          |       |       |   |
| FT3 5–95th percentile and TSH 5–95th percentile | 1.35 (0.97, 1.88) | 1.26 (0.92, 1.71) | 0.080 |
| FT3 >95th percentile and TSH 5–95th percentile | 1.94 (1.46, 2.58) | 0.62 (0.41, 0.93) | 0.02 |
| FT3 >95th percentile and TSH <5th percentile | 3.68 (1.94, 6.98) | 1.98 (0.92, 4.27) | 0.083 |
| FT3 <5th percentile and TSH 5–95th percentile | 0.82 (0.55, 1.21) | 1.20 (0.89, 1.62) | 0.222 |
| FT3 5–95th percentile and TSH >95th percentile | 1.13 (0.80, 1.60) | 1.54 (1.17, 2.03) | 0.002 |
| FT3 <5th percentile and TSH >95th percentile | 2.28 (0.67, 7.72) | 5.08 (2.13, 12.15) | <0.001 |
| **adjusted**            |       |       |   |
| FT3 5–95th percentile and TSH 5–95th percentile | 1.54 (1.09, 2.18) | 1.47 (1.06, 2.04) | 0.020 |
| FT3 >95th percentile and TSH 5–95th percentile | 2.25 (1.67, 3.03) | 0.64 (0.42, 0.97) | 0.035 |
| FT3 >95th percentile and TSH <5th percentile | 4.02 (2.05, 7.88) | 1.37 (0.58, 3.27) | 0.474 |
| FT3 <5th percentile and TSH 5–95th percentile | 0.75 (0.50, 1.13) | 1.01 (0.74, 1.39) | 0.937 |
| FT3 5–95th percentile and TSH >95th percentile | 1.08 (0.76, 1.55) | 1.40 (1.05, 1.87) | 0.021 |
| FT3 <5th percentile and TSH >95th percentile | 1.61 (0.43, 6.05) | 4.22 (1.59, 11.23) | 0.004 |

\[ ^a \] Adjusted for maternal age, gravidity, parity, gestational age, BMI, systolic and diastolic BP at delivery; GDM, ICP, PE, PIH, delivery mode, neonatal sex, FT4 and TPO-Ab positivity.

\[ ^b \] Additionally corrected for gestational age.

FT3, free triiodothyronine; TSH, thyroid stimulating hormone; PTB, preterm birth; FTB, full term birth; SGA/AGA, small/appropriate for gestational age; BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; FT4, free thyroxine; TPO-Ab, thyroid peroxidase antibody.
increased risk of PTB [33]. In contrast, Casey et al. showed no associations of PTB with maternal isolated hypothyroxinaemia, while Luawan et al. observed that hyperthyroidism increased the risk of PTB [34, 22]. In addition, both maternal hypothyroidism and hyperthyroidism had been reported to increase PTB risk in two cohort studies form US and Denmark [24, 35]. In the present study, we found that PTB was significantly associated with maternal hyperthyroidism, defined as cut-off points of the 5th and 95th percentiles, but not with other types of maternal dysfunction. A population-based cohort from the Netherlands indicated that a high FT4 level in early pregnancy, but not TSH level, are associated with LBW and an increased risk of SGA newborns in euthyroid women [13]. Another Dutch prospective cohort indicated that maternal TSH levels in the upper range of the reference interval in the first and third trimester are independently associated with an increased risk of SGA neonates at term; maternal FT4 levels and TPO-Ab positivity are not associated with SGA offspring [36]. A Spanish cohort study showed a significant inverse correlation of maternal FT4 and TSH levels at the first half of pregnancy with birthweight and indicated that high FT4 levels are associated with an increased risk of SGA [16]. In contrast, Su et al. suggested that maternal hypothyroxinemia (lower FT4 level) in the first 20 weeks of pregnancy increased the risk of SGA [9]. Our study showed that maternal hypothyroxinemia in late pregnancy is not associated with SGA, which had been reported earlier in two cohorts from Canada and Australia [37, 38]. Similarly, Casey et al. in the USA and Breathnach et al. in Ireland reported that maternal hypothyroxinemia is not associated with LBW and intrauterine growth restriction [34, 39]. In addition, we showed that higher FT4 levels (>95th percentile) decrease the risk of LGA, which is in agreement with the recent study by Zhu et al., who reported that higher FT4 levels reduce the birthweight and are inversely related to LGA risk [40]. Furthermore, we showed no significant association of FT4 levels with pregnancy complications (GDM/ICP/PIH) and adverse birth outcomes (PTB/SGA/LGA) after adjusting for maternal age and BMI, excluding PE (adjusted OR: 0.93, 95% CI: 0.88–0.99, p < 0.05).

At this time, existing studies examining the association of various forms of maternal thyroid dysfunction with adverse birth outcomes may not indicate consistent conclusions. This inconsistency may be due to study designs, sample sizes, the timing of blood sampling and tests, gestational age of the study subjects, maternal gestational weight gain, and socio-economic and iodine status. In addition, this can be attributed to the failure of some studies to adjust for maternal pregnancy complications, whereas the current study controlled for GDM, ICP, PE, and PIH. Additionally, different cut-off criteria defining thyroid dysfunction may contribute to this discrepancy. For example, FT4 <2.5th or FT4 <5th (even FT4 <10th) combined with normal TSH (2.5th–97.5th or 5th–95th or 10th–90th) were used to define isolated hypothyroxinaemia in different national cohorts. In addition, race/ethnicity may play an important role in modifying the potential risk of thyroid disorders during pregnancy because the risk of thyroid dysfunction in the population and predisposition to adverse pregnancy outcomes varies by race/ethnicity [41, 42].

Our findings provide new information on the adverse effect of higher maternal FT3 levels on fetal growth, which may contribute to a higher risk of PTB and SGA newborns. This large historical study gave us sufficient power to consider various potential confounders, including maternal pregnancy complications such as GDM and PE, which could affect birth outcomes. The impacts of maternal TPO-Ab status were considered when assessing the association of thyroid hormone levels with PTB, SGA, and LGA. In addition, after adjusting for available confounding factors, no significant correlation between maternal TPO-Ab positivity in late pregnancy and PTB, SGA, and LGA was observed, although a few studies have shown that maternal TPO-Ab positivity in the first and second trimester are independently associated with an increased risk of PTB and SGA [6, 33, 43, 44]. However, our study has several limitations. First, this was retrospective observational study conducted in a single centre and missing data (maternal socio-economic and iodine status) would contribute to possible bias in statistical analysis. Second, we did not have any data on whether the participants received thyroid medication before inclusion in the study, which may affect our results. Levothyroxine replacement therapy may be a common cause of hyperthyroxinaemia (high FT4 and normal TSH). Third, due to the lack of thyroid function values in early pregnancy in the study population, we did not evaluate persistent effects caused by maternal thyroid dysfunction from early pregnancy to late pregnancy. There may be abnormalities from the beginning in subjects with thyroid dysfunction in late pregnancy. The associations between adverse birth outcomes and persistent maternal thyroid dysfunction during pregnancy have been reported in recent studies [45, 46].

In conclusion, our study demonstrates that various maternal thyroid dysfunctions in late pregnancy are associated with different adverse birth outcomes and would recommend conventional screening of maternal thyroid function in late pregnancy as a potential method to predict fetal growth and birth, even in iodine rich regions of China.
Acknowledgments

We thank the staff of laboratory and medical record section in Changzhou maternity and child health care hospital for their help with technical assistance and information service.

Funding Sources

This work was supported by Changzhou Key Laboratory of High-tech Research (CM20193009), Changzhou science and technology support project (Social Development: CE20195040), and Jiangsu Maternal and Child Health Research Projects (F201842).

Conflicts of Interest

The authors have no potential conflicts of interest associated with this study.

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