# Thyroid peroxidase antibody titers, thyroid function, and iodine nutrition status of pregnant normotensive and preeclamptic women in Eastern Cape South Africa

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**BACKGROUND:** Autoimmune thyroid disease, one of the main risk factors for hypothyroidism, is associated with adverse pregnancy outcomes. The burden of autoimmune thyroid disease in pregnancy and its association with thyroid function among normotensive pregnant women and pregnant women with hypertension in South Africa are not known.

**OBJECTIVE:** This study aimed to establish the magnitude of thyroid peroxidase autoantibodies in pregnancy in the Eastern Cape of South Africa and its relationship with iodine nutrition status and preeclampsia.

**STUDY DESIGN:** Overall, 60 randomly selected normotensive pregnant controls at term and 120 pregnant participants with preeclampsia in the third trimester of pregnancy going to the Mthatha Regional Hospital and the Nelson Mandela Academic Hospital in the Eastern Cape Province who had complete data on thyroid peroxidase antibody titers, urinary iodine concentrations, serum thyroid-stimulating hormones, and free triiodothyronine, free thyroxine, and thyroglobulin levels were enrolled in this unmatched case-control study.

**RESULTS:** The cases and controls had similar mean chronological age (23.8 vs 24.0 years), body mass index (29.4 vs 28.8 kg/m$^2$), and median parity (both 1) ($P>.05$). The controls had a higher mean gestational age than participants with preeclampsia (38.5 vs 33.7 weeks, respectively; $P<.001$). Both participants with preeclampsia and normotensive participants had median thyroid peroxidase antibody levels consistent with a negative thyroid autoimmune status. Participants with preeclampsia had higher but nonstatistically significant median thyroid peroxidase antibody (2.14 vs 1.77 IU/L), thyroglobulin (25.9 vs 21.3 $\mu$g/L), and thyroid-stimulating hormone (2.4 vs 2.3 mIU/L) levels ($P>.05$) and significantly lower median urinary iodine concentration (123.4 vs 188.6 $\mu$g/L), free thyroxine (13.2 vs 14.1 pmol/L), and free triiodothyronine (4.3 vs 4.6 pmol/L) levels ($P<.05$) than normotensive controls. Thyroid peroxidase antibodies were positively correlated with thyroglobulin, urinary iodine concentration, and thyroid-stimulating hormone.

**CONCLUSION:** In the rural Eastern Cape of South Africa, pregnant women in the third trimester of pregnancy have thyroid peroxidase antibody titers that show negative thyroid autoimmune status. Insufficient iodine intake, other than thyroid autoimmune disease, seems to be the underlying cause of the lower free triiodothyronine and free thyroxine levels observed among women with preeclampsia.

**Key words:** iodine, preeclampsia, pregnancy, thyroid function, thyroid peroxidase antibody

## Introduction

Autoimmune thyroid disease (AITD) is the second most common cause of subclinical and overt hypothyroidism after an iodine-deficient diet.[1] The main thyroid autoantibodies are the antithyroid peroxidase antibodies (TPOAbs) and the antithyroglobulin antibodies (TgAbs). Among patients with AITD, TPOAbs are more prevalent than TgAbs.[1]

The TPOAbs lead to an increased risk of hypothyroidism through the destruction of the enzyme thyroid peroxidase, hence diminishing iodination of tyrosine residues on thyroglobulin (Tg) and eventual T3 and T4 outputs.[2] Hence, among pregnant women positive for TPOAbs, the increase in the

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The authors report no conflicting interest.

Informed consent was obtained from all mothers that were enrolled, and the study was conducted as stipulated in the Declaration of Helsinki.

The dataset for this study is available on request from the authors.

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## AJOG MFM at a Glance

### Why was this study conducted?

This study aimed to establish the magnitude of thyroid peroxidase autoantibodies in pregnancy in the Eastern Cape of South Africa and its relationship with iodine nutrition status and preeclampsia.

### Key findings

Both participants with preeclampsia and normotensive participants had comparable median serum thyroid peroxidase antibody (TPOAb) levels that were consistent with a negative thyroid autoimmune status. Participants with preeclampsia had significantly lower median urinary iodine concentration (UIC), free thyroxine, and free triiodothyronine ($P<.05$) but had nonsignificant higher levels of thyroglobulin (Tg) and thyroid-stimulating hormone (TSH) than normotensive controls ($P>.05$). Serum TPOAb levels were positively correlated with Tg, UIC, and TSH.

### What does this add to what is known?

Insufficient iodine intake, other than thyroid autoimmune disease, seems to be the underlying cause of diminished thyroid function and preeclampsia among pregnant women of African ancestry within the Eastern Cape of South Africa compared with pregnant women in other geographic settings.

production of thyroid hormones associated with the physiological changes of pregnancy will be inadequate, predisposing them to subclinical or overt hypothyroidism together with associated adverse pregnancy outcomes,[3–6] including miscarriages, preterm labor, abruptio placenta, increased perinatal morbidity and mortality, gestational hypertension and preeclampsia, and neonatal intensive care unit admissions.[5,6]

Both inadequate and excessive iodine intakes have been shown to be associated with an increased prevalence of TPOAbs.[7] Because of increased thyroid uptake of serum iodine to boost thyroid hormone output, a higher renal iodine filtration, and loss in urine and iodine transfer across the placenta to the fetus, pregnant women with inadequate iodine intake will be at increased risk of iodine deficiency.[8] This may create a vicious circle that augments the risk of TPOAb positivity, subclinical and overt hypothyroidism, and associated adverse pregnancy outcomes.

The prevalence of TPOAbs in pregnancy varies between 2% and 17%.[1] The serum levels of TPOAbs in pregnancy progressively reduce from the first trimester of pregnancy to the third trimester of pregnancy.[3,9] The prevalence rate of TPOAbs increases with maternal age.[10,11] To the best of our knowledge, no study has been conducted in South Africa to ascertain the prevalence of TPOAbs in pregnancy.

We conducted this pilot case-control study to ascertain the levels of serum TPOAbs and the relationship among spot urinary iodine concentration (UIC), serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), and Tg of normotensive pregnant women at term and women with preeclampsia in the third trimester of pregnancy. Spot UIC and serum Tg are measures of recent and protracted iodine nutritional status, respectively.

## Materials and Methods

### Study site

Participants were enrolled at Mthatha Regional Hospital, a 500-bed referral hospital, and Nelson Mandela Academic Hospital, an 800-bed tertiary and teaching hospital. The 2 hospitals deliver an average of 6700 and 4500 women annually, respectively. Both hospitals are located in OR Tambo Municipality, a rural district in the northern part of the Eastern Cape of South Africa. This area is characterized by iodine-deficient soils, yet more than 70% of the population are of low socioeconomic status, hence some use low-cost noniodized salt.[12,13]

### Study design

This was an unmatched case-control study to ascertain the serum levels of TPOAbs among normotensive pregnant participants and participants with preeclampsia of African ancestry and the relationship between TPOAbs and other thyroid function parameters of cases and controls. The data were collected between August 2018 and March 2020.

The cases were assigned the diagnosis of eclampsia, preeclampsia with or without severe features according to the International Society for the Study of Hypertension in Pregnancy guidelines.[14] Normotensive pregnant women admitted at term for elective or vaginal delivery were enrolled as controls.

### Inclusion and exclusion criteria

All consenting women who fulfilled the definition of cases or controls were eligible to participate in the study. Of note, 60 women with preeclampsia without severe features, 60 women with preeclampsia complicated with severe features or eclampsia, and 60 normotensive pregnant women at term, who had complete results of spot UIC, TSH, FT4, FT3, Tg, and TPOAb were randomly selected. Eligible participants who had incomplete data and those with a history of thyroid disease, chronic hypertension, or diabetes mellitus were excluded.

### Ethics approval

This study was approved by the Human Research Ethics Review Committee of Walter Sisulu University (reference number: 066/2017). Informed consent was obtained from all mothers who were enrolled, and the study was conducted as stipulated in the Declaration of Helsinki.

### Data collection

Using a structured questionnaire, we collected data that included the participants' age, parity, weeks of amenorrhea, previous obstetrical history, history of thyroid disease and diabetes mellitus, and previous medical or surgical treatment of thyroid disease or radiotherapy of the head and neck.

We used a portable electronic weighing scale with a portable height measuring board to obtain the weight and height of the participants according to standard procedures.[15] The blood pressure was determined according to the American Heart Association guidelines by taking the average of the 2 measurements obtained with an electronic sphygmomanometer at intervals of ≥2 minutes part.[16]

TSH, FT4, FT3, and Tg were assayed from venous blood collected at enrolment that was immediately centrifuged, and the serum was aliquoted and stored at −20°C until the time of analysis. The Roche-Hitachi cobas c system electrochemiluminescence immunoassay was used for determining the levels of serum TSH, FT4, and FT3. Serum TPOAb levels were measured with the Elabscience enzyme-linked immunosorbent assay (ELISA) kit. A cutoff TPOAb titer of >5.33 IU/L (the 95th percentile of 120 participants with a normally functioning thyroid gland) depicted a positive TPOAb status. The inductively coupled plasma mass spectrometry method was used to determine the UIC.[17]

## Statistical analysis

Data analysis was performed using the IBM SPSS Statistics software package for Windows (version 22; IBM Corporation, Chicago, IL). We used the Shapiro-Wilk test to check whether the data followed the normal distribution. The data were summarized as proportions (percentages) for categorical variables, means±standard deviations for normally distributed, and medians (25th−75th percentiles) for skewed continuous variables. The chi-square and Fisher exact tests were used to compare the distribution of categorical variables among cases and controls. The Student *t* test and the Mann-Whitney *U* test were used as appropriate for the comparison of continuous variables across groups. The Spearman correlation was used to determine relations between variables in the groups. A *P* value of <.05 was considered significant.

# Results

## General characteristics of the participants

Cases with preeclampsia and normotensive pregnant controls had comparable chronological age, body mass index, number of pregnancies (gravidity), and gestational age (GA) (*P*>.05) (Table 1). Participants with preeclampsia, having been enrolled soon after diagnosis, had significantly lower GA at enrolment than controls who by definition remained normotensive until delivery (33.7±5.1 and 38.5±1.8 weeks of amenorrhea, respectively; *P*<.001). The diastolic and systolic blood pressures at enrolment were anticipated as higher among cases than among controls (*P*<.001) (Table 1).

**TABLE 1**
**The general characteristics of normotensive pregnant women and women with preeclampsia or eclampsia**

| Variable | Normotensive (n=60) | Preeclampsia (n=120) | *P* value |
|---|---|---|---|
| Age (y) | 24.0±6.0 | 23.8±6.6 | .869 |
| BMI (kg/m$^2$) | 28.8±5.0 | 29.4±6.9 | .514 |
| Gravidity | 1 (1−2) | 1 (1−2) | .428[a] |
| GA at booking (WOA) | 21.0±4.8 | 21.6±4.6 | .434 |
| GA at enrolment (WOA) | 38.5±1.8 | 33.7±5.1 | <.001 |
| SBP (mm Hg) | 120.4±10.2 | 140.3±14.3 | <.001 |
| DBP (mm Hg) | 75.7±9.2 | 90.7±13.5 | <.001 |

Data are presented as mean±standard deviation or median (25th−75th percentiles), unless otherwise indicated.

*BMI*, body mass index; *DBP*, diastolic blood pressure; *GA*, gestational age; *SBP*, systolic blood pressure; *WOA*, weeks of amenorrhea.

[a] *P* value: Mann-Whitney *U* test was used.

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## Serum thyroid peroxidase antibody levels and other thyroid function parameters of cases and controls

The median (25th−75th percentiles) serum TPOAb for all 180 participants was 2.04 IU/L (1.16−4.38) with a range of 0.26 to 9.01 IU/L. The median serum TPOAb values were 1.77 IU/L (1.02−2.70), a range of 0.53 to 5.23 IU/L, for the 120 cases and 2.14 IU/L (1.32−3.30), a range of 0.26 to 9.01 IU/L, for the 60 controls. Pregnant women with preeclampsia had higher serum TPOAb values than normotensive pregnant women, but the result was not statistically significant (*P*=.064) (Table 2). Participants with preeclampsia had significantly lower serum FT4, FT3, and spot UIC values (*P*<.05) and higher but statistically nonsignificant serum Tg values than controls (*P*=.084) (Table 2 and Figure 1).

## Thyroid function status of the participants

Taking 4 mIU/L[18] as the upper normal value of TSH and 11.3 pmol/L as the lower limit of normal FT4,[19] participants with preeclampsia had higher proportions of thyroid hypofunction, but the difference was not statistically significant. The prevalence of the various thyroid function states for cases and controls were as follows: euthyroid (61.2% vs 76.6%), subclinical hypothyroidism (14.6% vs 11.7%), hypothyroxinemia (10.0% vs 19.0%), and overt hypothyroidism (5.2 vs 1.7%) (Table 3). The 7 patients with overt hypothyroidism (6 patients with preeclampsia and 1 normotensive patient) required further endocrinological assessment and care.

The median serum TPOAb titers for all euthyroid participants was 1.77 IU/L with 5th and 95th percentiles of 0.53 IU/L and 5.33 IU/L, respectively. Using TPOAb titer of >5.33 IU/L as the cutoff for TPOAb autoimmune positive status, as determined using the Elabscience ELISA kit in the current study,

**TABLE 2**
**Comparison of the thyroid function parameters—TPOAb, UIC, FT4, FT3, Tg, and TSH—of normotensive pregnant women and women with preeclampsia**

| Variable | Normotensive (n=60) | Preeclampsia (n=120) | *P* value[a] |
|---|---|---|---|
| TPOAb (IU/mL) | 1.77 (1.02–2.70) | 2.14 (1.32–3.30) | .064 |
| UIC (μg/L) | 188.6 (92.7–366.2) | 123.4 (55.9–338.5) | .020 |
| FT4 (pmol/L) | 14.1 (12.6–16.1) | 13.2 (11.4–15.1) | .019 |
| FT3 (pmol//L) | 4.6 (4.1–5.2) | 4.3 (3.6–4.9) | .005 |
| Tg (μg/L) | 21.3 (13.1–35.2) | 25.9 (15.6–47.1) | .084 |
| TSH (mIU/L) | 2.3 (1.8–3.1) | 2.4 (1.8–3.6) | .468 |

Data are presented as median (25th–75th percentiles), unless otherwise indicated.

*FT3*, free triiodothyronine; *FT4*, free thyroxine; *Tg*, thyroglobulin; *TPOAb*, thyroid peroxidase antibody; *TSH*, thyroid-stimulating hormone; *UIC*, urinary iodine concentration.

[a] *P* value: Mann-Whitney *U* test was used (normotensive vs preeclampsia).

*Businge. Iodine nutrition status other than thyroid autoimmunity associated with hypothyroxinemia and preeclampsia. Am J Obstet Gynecol Glob Rep 2023.*

all 60 normotensive pregnant controls were negative for TPOAbs, whereas 9 of 120 participants with preeclampsia (7.5%) were positive for TPOAbs (Table 4).

### Correlation between thyroid peroxidase antibodies and other variables

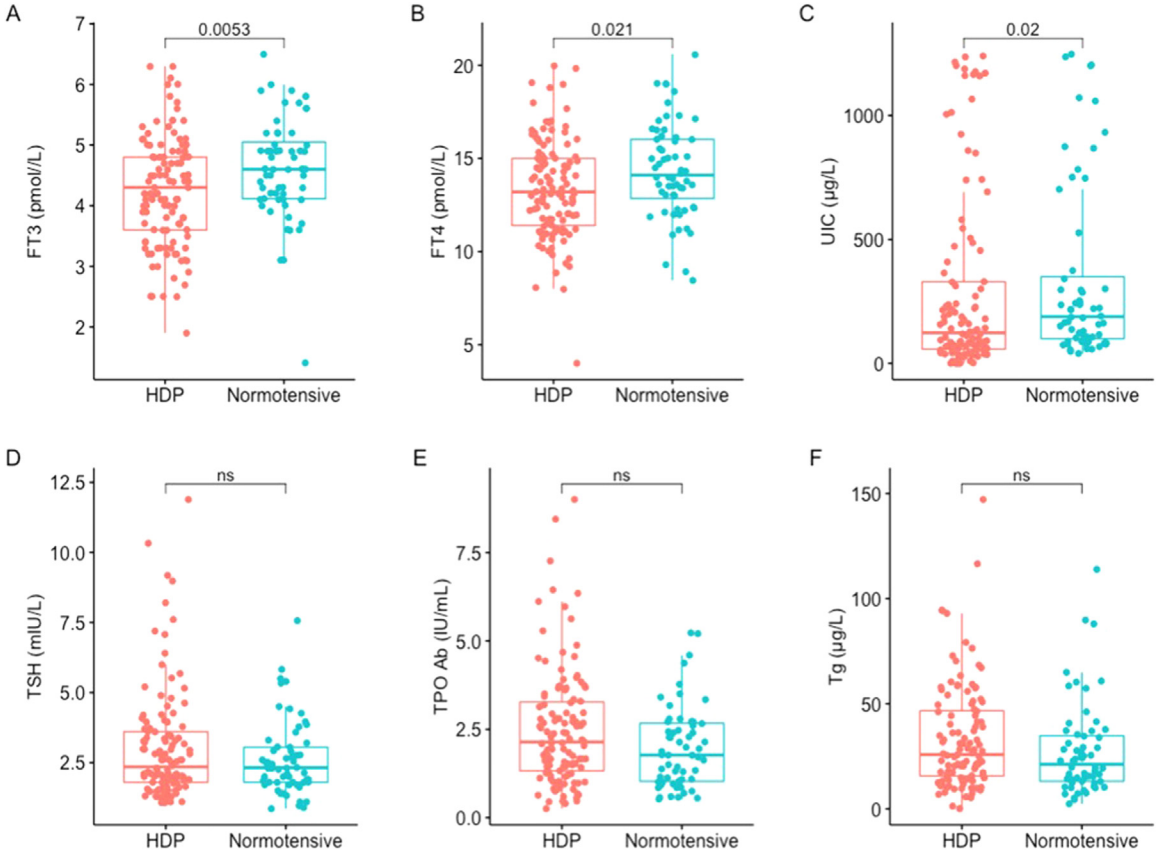
TPOAb titers were strongly correlated with serum Tg but mildly correlated with serum TSH and UIC. In addition, UIC was weakly correlated with serum FT3 (Table 5 and Figure 2).

## Discussion

### Principal findings

Here, we found that, in the rural Eastern Cape of South Africa, normotensive

**FIGURE 1**
**Comparisons of serum FT3, FT4, UIC, TSH, TPOAb, and Tg of women with preeclampsia (HDP) and normotensive pregnant women**




**A,** FT3. **B,** FT4. **C,** UIC. **D,** TSH. **E,** TPOab. **F,** Tg.

*FT3*, free triiodothyronine; *FT4*, free thyroxine; *HDP*, hypertensive disorders of pregnancy; *Tg*, thyroglobulin; *TPOab*, thyroid peroxidase antibody; *TSH*, thyroid-stimulating hormone; *UIC*, urinary iodine concentration.

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**TABLE 3**
**Thyroid function status of normotensive pregnant women and women with preeclampsia**

| Thyroid status | Normotensive | Preeclampsia | Chi-square | *P* value |
|---|---|---|---|---|
| | n (%) | n (%) | | |
| Euthyroid | 46 (76.6) | 71 (61.2) | 4.901 | .179 |
| SCH | 7 (11.7) | 17 (14.6) | | |
| Hypothyroxinemia | 6 (10.0) | 22 (19.0) | | |
| Overt hypothyroidism | 1(1.7) | 6 (5.2) | | |
| Total | 60 (100.0) | 116 (100.0) | | |

*SCH*, subclinical hypothyroidism.

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**TABLE 4**
**Thyroid peroxidase autoimmune status of normotensive pregnant women and women with preeclampsia**

| TPOAb autoimmune status | Normotensive | Preeclampsia | Fisher exact test *P* value |
|---|---|---|---|
| | n (%) | n (%) | |
| Negative | 60 (100.0) | 111 (92.5) | .03 |
| Positive | 0 (0) | 9 (7.5) | |
| Total | 60 (100.0) | 120 (100.0) | |

*TPOAb*, thyroid peroxidase antibody.

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pregnant women of African descent and 92.5% of women with preeclampsia, all in the third trimester of pregnancy, had median TPOAb titers that were consistent with a negative thyroid autoimmune status. This low prevalence of positive TPOAb status in the current study may partially be accounted for by ethnicity: a large study in the United States found a prevalence of a positive TPOAb status of 5.3% among participants of African descent compared with 13% in the entire sample.[11]

## Results in the context of what is known

Here, participants with preeclampsia had a higher but nonstatistically significant anti-TPOAb titer than normotensive participants. This finding is consistent with that of Alavi et al,[20] who found TPOAb titers within the normal range with no relationship between TPOAb levels and hypertensive disorders of pregnancy (HDPs). Other authors reported a higher but nonsignificant prevalence of HDPs among women who are positive for TPOAb antibodies than among women with a TPOAb negative status.[9,21] However, our results differ from those of Harshvardhan et al,[22] who found that the mean TPOAb levels of both participants with preeclampsia and normotensive pregnant participants were within the positive range for thyroid autoimmunity with participants with preeclampsia having a significantly higher TPOAb titer than normotensive pregnant participants.[22] This may be attributed to the high prevalence of thyroid autoimmunity in Asia and particularly a higher TPOAb positivity rate on the Indian subcontinent.[1]

In addition, the similarity or variation of our results from those of other authors may arise from different environmental exposures that are associated with thyroid autoimmunity.[2] These include urban residence, smoking cessation, and selenium deficiency. Iodine deficiency and excessive iodine supplementation have both been reported to increase the risk of AITD.[7]

## Clinical implications

Here, we found a strong positive correlation between Tg and TPOAb antibody titers (R=0.47; *P*<.0001) and a mild positive correlation with serum TSH (R=0.17; *P*=.022) and UIC (R=0.17; *P*=.024). As elevated Tg is a measure of long-term iodine deficiency and UIC a measure of recent iodine intake, it seems likely that iodine deficiency in the study population may predispose to some degree of thyroid autoimmunity. The weaker correlation of UIC with TPOAb compared with Tg may be due to high variation in UIC as a result of fluctuation in dietary iodine content and differential uptake of iodine by the thyroid gland that is subject to the degree of iodine deficiency[23] and the U-shaped relationship between iodine and TPOAb.[7] Previous research has reported higher TSH levels among participants positive for TPOAbs.[24] This may partially explain the observed mild correlation between TPOAb titers and serum TSH levels in the current study. In contrast, the relaxed negative feedback following prolonged iodine deficiency and reduced FT3 or FT4 from the thyroid may predispose to higher TSH output from the pituitary. This may lead to excessive thyrocyte stimulation, which, in the presence of environmental thyroid toxins, such as nitrate and thiocyanate, leads to diffuse necrosis of the thyroid cells, leading to lymphocyte infiltration and autoimmunity.[25]

Iodine deficiency and AITD are the leading causes of hypothyroidism.[1,26] Our study found that the serum thyroxine, the triiodothyronine, and the UIC of participants with preeclampsia were lower than those of normotensive pregnant participants. This may be attributed to inadequate iodine intake, which has been reported to be a risk factor for

**TABLE 5**
**Nonparametric correlation matrix of antiperoxidase antibodies (TPOAb), thyroid function biomarkers, age, and BMI**

| The Spearman rho correlation | | TPOAb | UIC | FT4 | FT3 | Tg | TSH | Age | BMI |
|---|---|---|---|---|---|---|---|---|---|
| TPOAb | Coefficient | | .173[a] | −.017 | .103 | .473[b] | .173[a] | .046 | .075 |
| | *P* value | | .024 | .821 | .172 | .000 | .022 | .541 | .317 |
| UIC | Coefficient | .173[a] | | .062 | .161[a] | −.026 | .039 | .047 | .058 |
| | *P* value | .024 | | .422 | .038 | .741 | .619 | .543 | .450 |
| FT4 | Coefficient | −.017 | .062 | | .433[b] | −.001 | −.048 | .227[b] | −.120 |
| | *P* value | .821 | .422 | | .000 | .994 | .523 | .002 | .114 |
| FT3 | Coefficient | .103 | .161 | .433[b] | | −.033 | .173[a] | −.013 | .084 |
| | *P* value | .172 | .038[a] | .000 | | .670 | .021 | .860 | .266 |
| Tg | Coefficient | .473[b] | −.026 | −.001 | −.033 | | .070 | −.271[b] | −.127 |
| | *P* value | .000 | .741 | .994 | .670 | | .361 | .000 | .097 |
| TSH | Coefficient | .173[a] | .039 | .523 | .021 | .070 | | .062 | .005 |
| | *P* value | .022 | .619 | .173[a] | .070 | .361 | | .412 | .943 |
| Age | Coefficient | .046 | .047 | .227[b] | −.013 | −.271[b] | .062 | | .237[b] |
| | *P* value | .541 | .543 | .002 | .860 | .000 | .412 | | .001 |
| BMI | Coefficient | .075 | .058 | −.120 | .084 | −.127 | .005 | .237[b] | |
| | *P* value | .317 | .450 | .114 | .266 | .097 | .943 | .001 | |

*BMI*, body mass index; *FT3*, triiodothyronine; *FT4*, thyroxine; *Tg*, thyroglobulin; *TPOAb*, thyroid peroxidase antibody; *TSH*, thyroid-stimulating hormone; *UIC*, urinary iodine concentration.

[a] $P<.05$; [b] $P<.01$.

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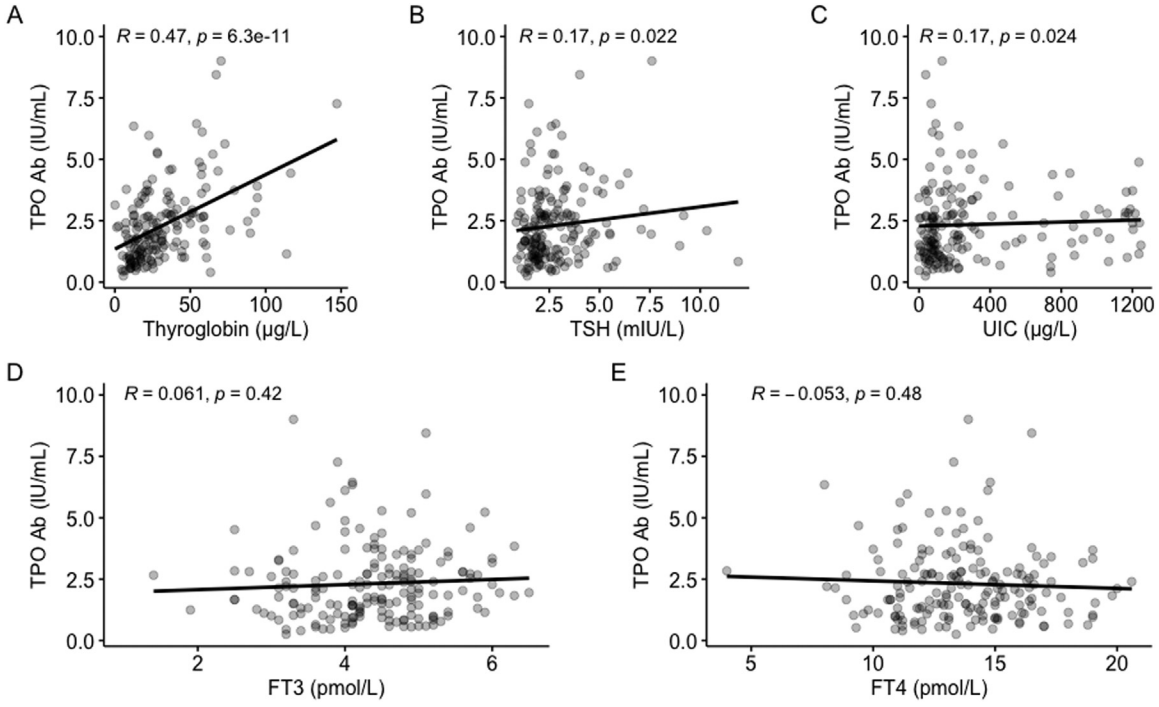
**FIGURE 2**
**Correlation between TPOAb levels and thyroglobulin, TSH, UIC, FT3, and FT4**




**A,** Thyroglobulin. **B,** TSH. **C,** UIC. **D,** FT3. **E,** FT4.

*FT3*, free triiodothyronine; *FT4*, free thyroxine; *TPOab*, thyroid peroxidase antibody; *TSH*, thyroid-stimulating hormone; *UIC*, urinary iodine concentration.

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preeclampsia and inadequate production of thyroid hormones.[26–28] However, the level of iodine deficiency among the participants with preeclampsia in the current study was mild and may explain the higher but nonstatistically significant levels of serum TSH and Tg in participants with preeclampsia than in normotensive pregnant participants.

## Research implications

Our study found that both normotensive pregnant women and women with preeclampsia had TPOAb titers in keeping with a negative thyroid AITD status. It is plausible that the lower thyroxine and triiodothyronine prevalence rates among participants with preeclampsia in our study population were due to insufficient iodine nutrition instead of thyroid autoimmunity. However, this requires further inquiry in other geographic settings.

## Strengths and limitations

Although our results are strengthened by concurrent analysis of iodine nutrition status, thyroid hormones, and TPOAb titers compared with previous studies, our study is limited by the small sample size and inability to assess the level of relevant environmental factors, such as selenium, nitrate, and thiocyanates.

## Conclusion

In the rural Eastern Cape of South Africa, pregnant women in the third trimester of pregnancy have TPOAb titers that show negative thyroid autoimmune status. Insufficient iodine intake, other than thyroid autoimmune disease, seems to be the underlying cause of the lower FT3 and FT4 levels observed among women with preeclampsia. ■

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